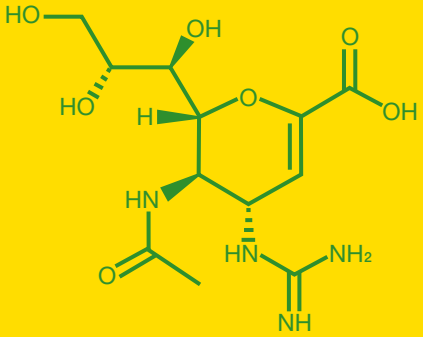


2016

# Nelson's Pediatric Antimicrobial Therapy

22nd Edition

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American Academy of Pediatrics

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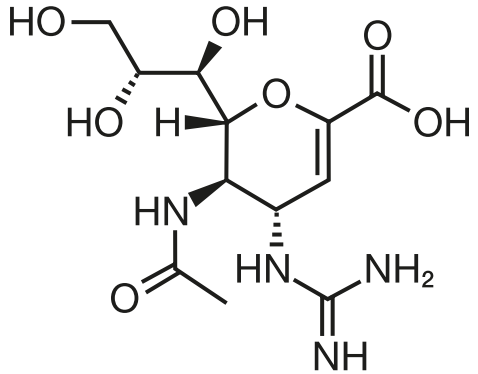


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## Contents

## Introduction

Welcome to the 22nd edition of the book John Nelson started in 1975 to help clinicians select the most appropriate therapy for children with infections! Our collaboration with the American Academy of Pediatrics (AAP) continues to be very productive as we learn more about how our book can address infectious diseases in childhood, the antimicrobials available to treat them, and how clinicians access accurate and relevant information as they care for children. We have had positive feedback from clinicians into why we select a particular drug at a particular dose. We are very pleased that many providers appreciate the references that we share in the print and app versions so that they can get all the relevant facts that go into our recommendations for therapy.

John Leake, our international health expert and the author of our chapter on parasitic infections for several years, now spends his time in laboratory medicine, developing tests for new and important diseases (like Ebola). However, we are extremely fortunate that Elizabeth Barnett, an expert in international/traveler health from the Boston University School of Medicine, is now joining us and, over the next editions, will give the chapter more of a focus on travel, immigrant, and refugee international health issues. She is the site director of the GeoSentinel Surveillance Network, created by the International Society of Travel Medicine and the US Centers for Disease Control and Prevention. She was recently appointed to the prestigious *Red Book*® Committee on Infectious Diseases of the AAP.

Jason Sauberan continues to carefully update the antimicrobial drugs and dosages for all children (Chapter 11), with particular attention to children with obesity (Chapter 12) and neonates (Chapter 5), which he writes with JB Cantey (under the watchful eye of Pablo Sanchez) and John van den Anker, a neonatologist/pharmacologist from Children's National Medical Center, who has again generously agreed to review our neonatal antibiotic chapter. Neonatal pharmacology of antimicrobials continues to be an area of intense study.

All of our editors have substantial clinical weeks "on service," which clearly shows in the insights provided by the antimicrobial recommendations, particularly for difficult infections. They are some of the best clinicians in the field of pediatric infectious diseases, all with academic interests in performing investigations to find out which newer as well as older agents work best to treat infections. They take the time to partner with the AAP and provide amazing advice in their particular areas of interest, knowledge, and experience.

The advice, experience, and knowledge of published/unpublished data are provided with a grading of our recommendations: our assessment of how strongly we feel about a recommendation and the strength of the evidence to support our recommendation (noted on the next page).

| Strength of Recommendation | Description |
|---|---|
| A | Strongly recommended |
| B | Recommended as a good choice |
| C | One option for therapy that is adequate, perhaps among many other adequate therapies |
| **Level of Evidence** | **Description** |
| I | Based on well-designed, prospective, randomized, and controlled studies in an appropriate population of children |
| II | Based on data derived from prospectively collected, small comparative trials, or noncomparative prospective trials, or reasonable retrospective data from clinical trials in children, or data from other populations (eg, adults) |
| III | Based on case reports, case series, consensus statements, or expert opinion for situations in which sound data do not exist |

As we state each year, many of the recommendations by the editors for specific situations have not been systematically evaluated in controlled, prospective, comparative clinical trials. Many of the recommendations may be supported by published data, but the data may never have been presented to or reviewed by the US Food and Drug Administration (FDA) and therefore are not in the package label. We in pediatrics find ourselves in this situation frequently. Many of us are working closely with the FDA to try to narrow the gap in our knowledge of antimicrobial agents between adults and children; the FDA is providing an exceptional effort to shed light on the doses that are safe and effective for children.

We are all deeply grateful for the hard work and tireless efforts of Alain Park, our AAP senior product development editor, who is our direct link to the considerable resources of the AAP and to all pediatric health care professionals. The AAP has reorganized its Department of Publishing, providing even more ways for us to share information with clinicians. We have wonderful supporters in the AAP departments of Publishing and Marketing and Sales—Jeff Mahony, Mark Grimes, Linda Smessaert, Peter Lynch, and the entire staff—who make certain that important clinical recommendations are provided to clinicians as effectively and effortlessly as possible.

John S. Bradley, MD

John D. Nelson, MD

# 1. Choosing Among Antibiotics Within a Class: Beta-lactams, Macrolides, Aminoglycosides, and Fluoroquinolones

New drugs should be compared with others in the same class regarding (1) antimicrobial spectrum; (2) degree of antibiotic exposure (a function of the pharmacokinetics of the nonprotein-bound drug at the site of infection and the pharmacodynamic properties of the drug); (3) demonstrated efficacy in adequate and well-controlled clinical trials; (4) tolerance, toxicity, and side effects; and (5) cost. If there is no substantial benefit for efficacy or safety, one should opt for using an older, more familiar, and less expensive drug with the narrowest spectrum of activity required to treat the infection.

## Beta-lactams

**Oral Cephalosporins** (cephalexin, cefadroxil, cefaclor, cefprozil, cefuroxime, cefixime, cefdinir, cefpodoxime, cefditoren [tablet only], and ceftibuten). As a class, the oral cephalosporins have the advantages over oral penicillins of somewhat greater spectrum of activity, greater safety, and greater palatability of the suspension formulations (penicillins have a bitter taste). The serum half-lives of cefpodoxime, ceftibuten, and cefixime are greater than 2 hours. This pharmacokinetic feature accounts for the fact that they may be given in 1 or 2 doses per day for certain indications, particularly otitis media, where the middle ear fluid half-life is likely to be much longer than the serum half-life. The spectrum of activity increases for gram-negative organisms as one goes from the first-generation cephalosporins (cephalexin and cefadroxil), to the second generation (cefaclor, cefprozil, and cefuroxime) that demonstrates activity against *Haemophilus influenzae* (including beta-lactamase–producing strains), to the third-generation agents (cefdinir, cefixime, cefpodoxime, and ceftibuten) that have enhanced coverage of many enteric gram-negative bacilli (*Escherichia coli, Klebsiella* spp). However, ceftibuten and cefixime in particular have a disadvantage of less activity against *Streptococcus pneumoniae* than the others, particularly against penicillin (beta-lactam) non-susceptible strains. None of the currently available oral cephalosporins have activity against *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* (MRSA). The palatability of generic versions of these products may not have the same pleasant characteristics as the original products.

**Parenteral Cephalosporins.** First-generation cephalosporins, such as cefazolin, are used mainly for treatment of gram-positive infections (excluding MRSA) and for surgical prophylaxis; the gram-negative spectrum is limited. Cefazolin is well tolerated on intramuscular or intravenous injection.

A second-generation cephalosporin (cefuroxime) and the cephamycins (cefoxitin and cefotetan) provide increased activity against many gram-negative organisms, particularly *Haemophilus* and *E coli*. Cefoxitin has, in addition, activity against approximately 80% of strains of *Bacteroides fragilis* and can be considered for use in place of metronidazole, clindamycin, or carbapenems when that organism is implicated in non–life-threatening disease.

Third-generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) all have enhanced potency against many enteric gram-negative bacilli. They are inactive against enterococci and *Listeria* and only ceftazidime has significant activity against *Pseudomonas*. Cefotaxime and ceftriaxone have been used very successfully to treat meningitis caused by pneumococcus (mostly penicillin-susceptible strains), *H influenzae* type b (Hib), meningococcus, and susceptible strains of *E coli* meningitis in a small number of young infants. These drugs have the greatest usefulness for treating gram-negative bacillary infections due to their safety, compared with other classes of antibiotics. Because ceftriaxone is excreted to a large extent via the liver, it can be used with little dosage adjustment in patients with renal failure. Furthermore, it has a serum half-life of 4 to 7 hours and can be given once a day for all infections, including meningitis, that are caused by susceptible organisms.

Cefepime, a fourth-generation cephalosporin approved for use in children, exhibits the antipseudomonal activity of ceftazidime, the gram-positive activity of second-generation cephalosporins, and better activity against gram-negative enteric bacilli such as *Enterobacter* and *Serratia* than is documented with cefotaxime and ceftriaxone.

Ceftaroline is a fifth-generation cephalosporin, the first of the cephalosporins with activity against MRSA. Ceftaroline was approved by the US Food and Drug Administration (FDA) in December 2010 for adults with complicated skin infections (including MRSA) and community-acquired pneumonia (with insufficient numbers of adult patients with MRSA pneumonia to be able to comment on efficacy). The pharmacokinetics of ceftaroline have been evaluated in all pediatric age groups, including neonates; clinical studies for community-acquired pneumonia and complicated skin infection have been completed in children; and studies in neonatal sepsis are in progress.

**Penicillinase-Resistant Penicillins** (dicloxacillin [capsules only]; nafcillin and oxacillin [parenteral only]). "Penicillinase" refers specifically to the beta-lactamase produced by *S aureus* in this case and not those produced by gram-negative bacteria. These antibiotics are active against penicillin-resistant *S aureus* but not against MRSA. Nafcillin differs pharmacologically from the others in being excreted primarily by the liver rather than by the kidneys, which may explain the relative lack of nephrotoxicity compared with methicillin, which is no longer available in the United States. Nafcillin pharmacokinetics are erratic in persons with liver disease.

**Antipseudomonal Beta-lactams** (ticarcillin/clavulanate, piperacillin, piperacillin/tazobactam, aztreonam, ceftazidime, cefepime, meropenem, and imipenem). Timentin (ticarcillin/clavulanate) and Zosyn (piperacillin/tazobactam) represent combinations of 2 beta-lactam drugs. One beta-lactam drug in the combination, known as a "beta-lactamase inhibitor" (clavulanic acid or tazobactam in these combinations), binds irreversibly to and neutralizes specific beta-lactamase enzymes produced by the organism, allowing the second beta-lactam drug (ticarcillin or piperacillin) to act as the active antibiotic to bind effectively to the intracellular target site (transpeptidase), resulting in death of the organism. Thus, the combination only adds to the spectrum of the original antibiotic

when the mechanism of resistance is a beta-lactamase enzyme and only when the beta-lactamase inhibitor is capable of binding to and inhibiting that particular organism's beta-lactamase enzyme. The combinations extend the spectrum of activity of the primary antibiotic to include many beta-lactamase–positive bacteria, including some strains of enteric gram-negative bacilli (*E coli, Klebsiella,* and *Enterobacter*), *S aureus,* and *B fragilis.* Ticarcillin/clavulanate and piperacillin/tazobactam have no significant activity against *Pseudomonas* beyond that of ticarcillin or piperacillin because their beta-lactamase inhibitors do not effectively inhibit all of the many relevant beta-lactamases of *Pseudomonas.*

*Pseudomonas* has an intrinsic capacity to develop resistance following exposure to any beta-lactam, based on the activity of several inducible chromosomal beta-lactamases, upregulated efflux pumps, and changes in the permeability of the cell wall. Because development of resistance during therapy is not uncommon (particularly beta-lactamase–mediated resistance against ticarcillin, piperacillin, or ceftazidime), an aminoglycoside such as tobramycin is often used in combination, in hopes that the tobramycin will kill strains developing resistance to the beta-lactams. Cefepime, meropenem, and imipenem are relatively stable to the beta-lactamases induced while on therapy and can be used as single-agent therapy for most *Pseudomonas* infections, but resistance may still develop to these agents based on other mechanisms of resistance. For *Pseudomonas* infections in compromised hosts or in life-threatening infections, these drugs, too, should be used in combination with an aminoglycoside or a second active agent.

**Aminopenicillins** (amoxicillin and amoxicillin/clavulanate [oral formulations only, in the United States], ampicillin [oral and parenteral], and ampicillin/sulbactam [parenteral only]). Amoxicillin is very well absorbed, good tasting, and associated with very few side effects. Augmentin is a combination of amoxicillin and clavulanate (see Antipseudomonal Beta-lactams for more information on beta-lactam/beta-lactamase inhibitor combinations) that is available in several fixed proportions that permit amoxicillin to remain active against many beta-lactamase–producing bacteria, including *H influenzae* and *S aureus* (but not MRSA). Amoxicillin/clavulanate has undergone many changes in formulation since its introduction. The ratio of amoxicillin to clavulanate was originally 4:1, based on susceptibility data of pneumococcus and *Haemophilus* during the 1970s. With the emergence of penicillin-resistant pneumococcus, recommendations for increasing the dosage of amoxicillin, particularly for upper respiratory tract infections, were made. However, if one increases the dosage of clavulanate even slightly, the incidence of diarrhea increases dramatically. If one keeps the dosage of clavulanate constant while increasing the dosage of amoxicillin, one can treat the relatively resistant pneumococci while not increasing gastrointestinal side effects of the combination. The original 4:1 ratio is present in suspensions containing 125-mg and 250-mg amoxicillin/5 mL and the 125-mg and 250-mg chewable tablets. A higher 7:1 ratio is present in the suspensions containing 200-mg and 400-mg amoxicillin/5 mL and in the 200-mg and 400-mg chewable tablets. A still higher ratio of 14:1 is present in the suspension formulation Augmentin ES-600 that contains 600-mg amoxicillin/5 mL; this preparation is designed to deliver 90 mg/kg/day of amoxicillin, divided twice daily, for the treatment of ear (and sinus) infections. The

high serum and middle ear fluid concentrations achieved with 45 mg/kg/dose, combined with the long middle ear fluid half-life of amoxicillin, allow for a therapeutic antibiotic exposure to pathogens in the middle ear with a twice-daily regimen. However, the prolonged half-life in the middle ear fluid is not necessarily found in other infection sites (eg, skin, lung tissue, joint tissue), for which dosing of amoxicillin and Augmentin should continue to be 3 times daily for most susceptible pathogens.

For older children who can swallow tablets, the amoxicillin to clavulanate ratios are as follows: 500-mg tablet (4:1); 875-mg tablet (7:1); 1,000-mg tablet (16:1).

Sulbactam, another beta-lactamase inhibitor like clavulanate, is combined with ampicillin in the parenteral formulation Unasyn. The cautions regarding spectrum of activity for Timentin and Zosyn with respect to the limitations of the beta-lactamase inhibitor in increasing the spectrum of activity (see Antipseudomonal Beta-lactams) also apply to Unasyn.

**Carbapenems.** Meropenem, imipenem, doripenem, and ertapenem are carbapenems with a broader spectrum of activity than any other class of beta-lactam currently available. Meropenem, imipenem, and ertapenem are approved by the FDA for use in children, while doripenem is under investigation in children. At present, we recommend them for treatment of infections caused by bacteria resistant to standard therapy or for mixed infections involving aerobes and anaerobes. Imipenem has greater central nervous system irritability compared with other carbapenems, leading to an increased risk of seizures in children with meningitis. Meropenem was not associated with an increased rate of seizures, compared with cefotaxime in children with meningitis. Imipenem and meropenem are active against virtually all coliform bacilli, including cefotaxime-resistant (extended spectrum beta-lactamase–producing or ampC-producing) strains, against *Pseudomonas aeruginosa* (including most ceftazidime-resistant strains), and against anaerobes, including *B fragilis*. While ertapenem lacks the excellent activity against *P aeruginosa* of the other carbapenems, it has the advantage of a prolonged serum half-life, which allows for once-daily dosing in adults and children aged 13 years and older and twice-daily dosing in younger children. Newly emergent strains of *Klebsiella pneumoniae* contain *K pneumoniae* carbapenemases that degrade and inactivate all the carbapenems. These strains, as well as strains carrying the less common New Delhi metallo-beta-lactamase (also active against carbapenems), have begun to spread to many parts of the world, reinforcing the need to keep track of your local antibiotic susceptibility patterns.

## Macrolides

Erythromycin is the prototype of macrolide antibiotics. Almost 30 macrolides have been produced, but only 3 are FDA approved for children in the United States: erythromycin, azithromycin (also called an azalide), and clarithromycin, while a fourth, telithromycin (also called a ketolide), is approved for adults and only available in tablet form. As a class, these drugs achieve greater concentrations in tissues than in serum, particularly with azithromycin and clarithromycin. As a result, measuring serum concentrations is

usually not clinically useful. Gastrointestinal intolerance to erythromycin is caused by the breakdown products of the macrolide ring structure. This is much less of a problem with azithromycin and clarithromycin. Azithromycin, clarithromycin, and telithromycin extend the activity of erythromycin to include *Haemophilus;* azithromycin and clarithromycin also have substantial activity against certain mycobacteria. Azithromycin is also active in vitro and effective against many enteric gram-negative pathogens, including *Salmonella* and *Shigella.* Solithromycin, a fluoro-ketolide with enhanced activity against gram-positive organisms, including MRSA, is currently in pediatric clinical trials.

## Aminoglycosides

Although 5 aminoglycoside antibiotics are available in the United States, only 3 are widely used for systemic therapy of aerobic gram-negative infections and for synergy in the treatment of certain gram-positive infections: gentamicin, tobramycin, and amikacin. Streptomycin and kanamycin have more limited utility due to increased toxicity compared with the other agents. Resistance in gram-negative bacilli to aminoglycosides is caused by bacterial enzymes that adenylate, acetylate, or phosphorylate the aminoglycoside, resulting in inactivity. The specific activities of each enzyme against each agent in each pathogen are highly variable. As a result, antibiotic susceptibility tests must be done for each aminoglycoside drug separately. There are small differences in toxicities to the kidneys and eighth cranial nerve hearing/vestibular function, although it is uncertain whether these small differences are clinically significant. For all children receiving a full treatment course, it is advisable to monitor peak and trough serum concentrations early in the course of therapy, as the degree of drug exposure correlates with toxicity and elevated trough concentrations may predict impending drug accumulation. With amikacin, desired peak concentrations are 20 to 35 μg/mL and trough drug concentrations are less than 10 μg/mL; for gentamicin and tobramycin, depending on the frequency of dosing, peak concentrations should be 5 to 10 μg/mL and trough concentrations less than 2 μg/mL. Children with cystic fibrosis require greater dosages to achieve equivalent therapeutic serum concentrations due to enhanced clearance. Inhaled tobramycin has been very successful in children with cystic fibrosis as an adjunctive therapy of gram-negative bacillary infections. The role of inhaled aminoglycosides in other gram-negative pneumonias (eg, ventilator-associated pneumonia) has not yet been defined.

**Once-Daily Dosing of Aminoglycosides.** Once-daily dosing of 5 to 7.5 mg/kg gentamicin or tobramycin has been studied in adults and in some neonates and children; peak serum concentrations are greater than those achieved with dosing 3 times daily. Aminoglycosides demonstrate concentration-dependent killing of pathogens, suggesting a potential benefit to higher serum concentrations achieved with once-daily dosing. Regimens giving the daily dosage as a single infusion, rather than as traditionally split doses every 8 hours, are effective and safe for normal adult hosts and immune-compromised hosts with fever and neutropenia and may be less toxic. Experience with once-daily dosing in children is increasing, with similar results as noted for adults. Once-daily dosing should be considered as effective as multiple, smaller doses per day and may be safer for children.

## Fluoroquinolones

More than 30 years ago, fluoroquinolone (FQ) toxicity to cartilage in weight-bearing joints in experimental juvenile animals was documented to be dose and duration of therapy dependent. Pediatric studies were, therefore, not initially undertaken with ciprofloxacin or other FQs. However, with increasing antibiotic resistance in pediatric pathogens and an accumulating database in pediatrics suggesting that joint toxicity may be uncommon, the FDA allowed prospective studies to proceed in 1998. As of July 2015, no cases of documented FQ-attributable joint toxicity have occurred in children with FQs that are approved for use in the United States. However, no published data are available from prospective, blinded studies to accurately assess this risk. Unblinded studies with levofloxacin for respiratory tract infections and unpublished randomized studies comparing ciprofloxacin versus other agents for complicated urinary tract infection suggest the possibility of uncommon, reversible, FQ-attributable arthralgia, but these data should be interpreted with caution. Prospective, randomized, double-blind studies of moxifloxacin, in which cartilage injury is being assessed, are currently underway. The use of FQs in situations of antibiotic resistance where no other active agent is available is reasonable, weighing the benefits of treatment against the low risk of toxicity of this class of antibiotics. The use of an oral FQ in situations in which the only alternative is parenteral therapy is also justified (Bradley JS, et al. *Pediatrics.* 2011;128[4]:e1034–e1045).

Ciprofloxacin usually has very good gram-negative activity (with great regional variation in susceptibility) against enteric bacilli (*E coli, Klebsiella, Enterobacter, Salmonella,* and *Shigella*) and against *P aeruginosa.* However, it lacks substantial gram-positive coverage and should not be used to treat streptococcal, staphylococcal, or pneumococcal infections. Newer-generation FQs are more active against these pathogens; levofloxacin has documented efficacy and short-term safety in pediatric clinical trials for respiratory tract infections (acute otitis media and community-acquired pneumonia). None of the newer-generation FQs are more active against gram-negative pathogens than ciprofloxacin. Quinolone antibiotics are bitter tasting. Ciprofloxacin and levofloxacin are currently available in a suspension form; ciprofloxacin is FDA approved in pediatrics for complicated urinary tract infections and inhalation anthrax, while levofloxacin is approved for inhalation anthrax only, as the sponsor chose not to apply for approval for pediatric respiratory tract infections. For reasons of safety and to prevent the emergence of widespread resistance, FQs should still not be used for primary therapy of pediatric infections and should be limited to situations in which safe and effective oral therapy with other classes of antibiotics does not exist.

## 2. Choosing Among Antifungal Agents: Polyenes, Azoles, and Echinocandins

Separating antifungal agents by class, much like navigating the myriad of antibacterial agents, allows one to best understand the underlying mechanisms of action and then appropriately choose which agent would be optimal for empirical therapy or a targeted approach. There are certain helpful generalizations that should be considered, eg, echinocandins are fungicidal against yeast and fungistatic against molds, while azoles are the opposite. Coupled with these concepts is the need for continued surveillance for fungal resistance patterns. While some fungal species are inherently or very often resistant to specific agents or even classes, there are also an increasing number of fungal isolates that are developing resistance due to environmental pressure or chronic use in individual patients. In 2016, there are 14 individual antifungal agents approved by the US Food and Drug Administration (FDA) for systemic use, and for each agent there are often several formulations (each with unique pharmacokinetics that one has to understand to optimize the agent, particularly in patients who are critically ill). Therefore, it is more important than ever to establish a firm foundation in understanding how these antifungal agents work and where they work best.

### Polyenes

**Amphotericin B** (AmB) is a polyene antifungal antibiotic that has been available since 1958 for the treatment of invasive fungal infections. Its name originates from the drug's amphoteric property of reacting as an acid as well as a base. Nystatin is another polyene antifungal, but, due to systemic toxicity, it is only used in topical preparations. It was named after the research laboratory where it was discovered, the New York State Health Department Laboratory. AmB remains the most broad-spectrum antifungal available for clinical use. This lipophilic drug binds to ergosterol, the major sterol in the fungal cell membrane, and creates transmembrane pores that compromise the integrity of the cell membrane and create a rapid fungicidal effect through osmotic lysis. Toxicity is likely due to the cross-reactivity with the human cholesterol bi-lipid membrane, which resembles ergosterol. The toxicity of the conventional formulation, AmB deoxycholate (AmB-D), can be substantial from the standpoints of systemic reactions (fever, rigors) and acute and chronic renal toxicity. Premedication with acetaminophen, diphenhydramine, and meperidine is often required to prevent systemic reactions during infusion. Renal dysfunction manifests primarily as decreased glomerular filtration with a rising serum creatinine concentration, but substantial tubular nephropathy is associated with potassium and magnesium wasting, requiring supplemental potassium for many neonates and children, regardless of clinical symptoms associated with infusion. Fluid loading with saline pre– and post–AmB-D infusion seems to mitigate renal toxicity.

Three lipid preparations approved in the mid-1990s decrease toxicity with no apparent decrease in clinical efficacy. Decisions on which lipid AmB preparation to use should, therefore, largely focus on side effects and costs. Two clinically useful lipid formulations exist: one in which ribbon-like lipid complexes of AmB are created (amphotericin B lipid

complex [ABLC]), Abelcet, and one in which AmB is incorporated into true liposomes (liposomal amphotericin B [L-AmB]), AmBisome. The standard dosage used of these preparations is 5 mg/kg/day, in contrast to the 1 mg/kg/day of AmB-D. In most studies, the side effects of L-AmB were somewhat less than those of ABLC, but both have significantly fewer side effects than AmB-D. The advantage of the lipid preparations is the ability to safely deliver a greater overall dose of the parent AmB drug. The cost of conventional AmB-D is substantially less than either lipid formulation. A colloidal dispersion of AmB in cholesteryl sulfate, Amphotec, is also available, with decreased nephrotoxicity, but infusion-related side effects are closer to AmB-D than to the lipid formulations and preclude recommendation for its use. The decreased nephrotoxicity of the 3 lipid preparations is thought to be due to the preferential binding of its AmB to high-density lipoproteins, compared with AmB-D binding to low-density lipoproteins. Despite in vitro concentration-dependent killing, a clinical trial comparing L-AmB at doses of 3 mg/kg/day versus 10 mg/kg/day found no efficacy benefit for the higher dose and only greater toxicity.[1] Therefore, it is generally not recommended to use any AmB preparations at very high dosages (>5 mg/kg/day), as it will likely only incur greater toxicity with no real therapeutic advantage. There are reports of using higher dosing in very difficult infections where AmB is the first-line therapy (eg, mucormycosis), and while experts remain divided on this practice, it is clear that at least 5 mg/kg/day of a lipid AmB formulation should be used. AmB has a long terminal half-life and, coupled with the concentration-dependent killing, the agent is best used as single daily doses. These pharmacokinetics explain the use in some studies of once-weekly AmB for antifungal prophylaxis. If the overall AmB exposure needs to be decreased due to toxicity, it is best to increase the dosing interval (eg, 3 times weekly) but retain the full mg/kg dose for optimal pharmacokinetics.

AmB-D has been used for nonsystemic purposes, such as in bladder washes, intraventricular instillation, intrapleural instillation, and other modalities, but there are no firm data supporting those clinical indications, and it is likely that the local toxicities outweigh the theoretical benefits. One exception is aerosolized AmB for antifungal prophylaxis (not treatment) in lung transplant recipients due to the different pathophysiology of invasive aspergillosis (often originating at the bronchial anastomotic site, more so than parenchymal disease) in that specific patient population. Due to the lipid chemistry, the L-AmB does not interact well with renal tubules and L-AmB is recovered from the urine at lower levels than AmB-D, so there is a theoretic concern with using a lipid formulation, as opposed to AmB-D, when treating isolated urinary fungal disease. This theoretic concern is likely outweighed by the real concern of toxicity with AmB-D. Most experts believe AmB-D should be reserved for use in resource-limited settings in which no alternative agents (eg, lipid formulations) are available. An exception might be in neonates, where limited retrospective data suggest that the AmB-D formulation had better efficacy.[2] Importantly, there are several pathogens that are inherently or functionally resistant to AmB, including *Candida lusitaniae, Trichosporon* spp, *Aspergillus terreus, Fusarium* spp, and *Pseudallescheria boydii* (*Scedosporium apiospermum*) or *Scedosporium prolificans.*

## Azoles

This class of systemic agents was first approved in 1981 and is divided into imidazoles (ketoconazole), triazoles (fluconazole, itraconazole), and second-generation triazoles (voriconazole, posaconazole, and isavuconazole) based on the number of nitrogen atoms in the azole ring. All of the azoles work by inhibition of ergosterol synthesis (fungal cytochrome P450 [CYP] sterol 14-demethylation) that is required for fungal cell membrane integrity. While the polyenes are rapidly fungicidal, the azoles are fungistatic against yeasts and fungicidal against molds. However, it is important to note that ketoconazole and fluconazole have no mold activity. The only systemic imidazole is ketoconazole, which is primarily active against *Candida* spp and is available in an oral formulation. Three azoles (itraconazole, voriconazole, posaconazole) need therapeutic drug monitoring with trough levels within the first 4 to 7 days (when patient is at pharmacokinetic steady-state); it is unclear at present if isavuconazole will require drug-level monitoring. It is less clear if therapeutic drug monitoring is required during primary azole prophylaxis, although low levels have been associated with a higher probability of breakthrough infection.

**Fluconazole** is active against a broader range of fungi than ketoconazole and includes clinically relevant activity against *Cryptococcus, Coccidioides,* and *Histoplasma.* Like most other azoles, fluconazole requires a double loading dose on the first day, which has been nicely studied in neonates[3] and is likely also required, but not definitively proven yet, in all children. Fluconazole achieves relatively high concentrations in urine and cerebrospinal fluid (CSF) compared with AmB due to its low lipophilicity, with urinary concentrations often so high that treatment against even "resistant" pathogens that are isolated only in the urine is possible. Fluconazole remains one of the most active, and so far one of the safest, systemic antifungal agents for the treatment of most *Candida* infections. *Candida albicans* remains generally sensitive to fluconazole, although some resistance is present in many non-*albicans Candida* spp as well as in *C albicans* in children repeatedly exposed to fluconazole. For instance, *Candida krusei* is considered inherently resistant to fluconazole, and *Candida glabrata* demonstrates dose-dependent resistance to fluconazole (and usually voriconazole). Fluconazole is available in parenteral and oral (with >90% bioavailability) formulations and toxicity is unusual and primarily hepatic.

**Itraconazole** is active against an even broader range of fungi and, unlike fluconazole, includes molds such as *Aspergillus.* It is currently available as a capsule or oral solution (the intravenous [IV] form was discontinued); the oral solution provides higher, more consistent serum concentrations than capsules and should be used preferentially. Absorption using itraconazole oral solution is improved on an empty stomach (unlike the capsule form, which is best administered under fed conditions), and monitoring itraconazole serum concentrations, like most azole antifungals, is a key principal in management (generally itraconazole trough levels should be >0.5–1 μg/mL; trough levels >3 μg/mL may be associated with increased toxicity). In adult patients, itraconazole is recommended to be loaded at 200 mg twice daily for 2 days, followed by 200 mg daily starting on the

third day. Dosing in children requires twice-daily dosing throughout treatment. Limited pharmacokinetic data are available in children; itraconazole has not been approved by the FDA for pediatric indications. Itraconazole is indicated in adults for therapy of mild/moderate disease with blastomycosis, histoplasmosis, and others. Although it possesses antifungal activity, itraconazole is not indicated as primary therapy against invasive aspergillosis, as voriconazole is a far superior option. Itraconazole is not active against *Zygomycetes* (eg, mucormycosis). Toxicity in adults is primarily hepatic.

**Voriconazole** was approved in 2002 and is only FDA approved for children 12 years and older, although there are now substantial pharmacokinetic data and experience for children aged 2 to 12 years.[4] Voriconazole is a fluconazole derivative, so think of it as having the greater tissue and CSF penetration of fluconazole but the added antifungal spectrum to include molds. While the bioavailability of voriconazole in adults is approximately 96%, multiple studies have shown that it is only approximately 50% in children, requiring clinicians to carefully monitor voriconazole trough concentrations in patients taking the oral formulation, further complicated by great inter-patient variability in clearance. Voriconazole serum concentrations are tricky to interpret, but monitoring concentrations is essential to using this drug, like all azole antifungals, and especially important in circumstances of suspected treatment failure or possible toxicity. Most experts suggest voriconazole trough concentrations of 2 μg/mL (at a minimum, 1 μg/mL) or greater, which would generally exceed the pathogen's minimum inhibitory concentration, but generally toxicity will not be seen until concentrations of approximately 6 μg/mL or greater. One important point is the acquisition of an accurate trough concentration, one obtained just before the next dose is due and not obtained through a catheter infusing the drug. These simple trough parameters will make interpretation possible. The fundamental voriconazole pharmacokinetics are different in adults versus children; in adults, voriconazole is metabolized in a nonlinear fashion, whereas in children, the drug is metabolized in a linear fashion. This explains the increased pediatric starting dosing for voriconazole at 9 mg/kg/dose versus loading with 6 mg/kg/dose in adult patients. Younger children, especially, require even higher dosages of voriconazole and also have a larger therapeutic window for dosing. However, many studies have shown an inconsistent relationship between dosing and levels, highlighting the need for close monitoring after the initial dosing scheme and then dose adjustment as needed. Given the poor clinical and microbiological response of *Aspergillus* infections to AmB, voriconazole is now the treatment of choice for invasive aspergillosis and many other mold infections (eg, pseudallescheriasis, fusariosis). Importantly, infections with *Zygomycetes* (eg, mucormycosis) are resistant to voriconazole. Voriconazole retains activity against most *Candida* spp, including some that are fluconazole resistant, but it is unlikely to replace fluconazole for treatment of fluconazole-susceptible *Candida* infections. Importantly, there are increasing reports of *C glabrata* resistance to voriconazole. Voriconazole produces some unique transient visual field abnormalities in about 10% of adults and children. There are an increasing number of reports, seen in as high as 20% of patients, of a photosensitive sunburn-like erythema that is not aided by sunscreen (only sun avoidance). In some rare long-term (mean of 3 years of therapy) cases, this voriconazole phototoxicity has developed into cutaneous squamous

cell carcinoma. Discontinuing voriconazole is recommended in patients experiencing chronic phototoxicity. The rash is the most common indication for switching from voriconazole to posaconazole/isavuconazole if a triazole antifungal is required. Hepatotoxicity is uncommon, occurring only in 2% to 5% of patients. Voriconazole is CYP metabolized (CYP2C19), and allelic polymorphisms in the population have shown that some Asian patients will achieve higher toxic serum concentrations than other patients. Voriconazole also interacts with many similarly P450 metabolized drugs to produce some profound changes in serum concentrations of many concurrently administered drugs.

**Posaconazole,** an itraconazole derivative, was FDA approved in 2006 as an oral suspension for children 13 years and older. An extended-release tablet formulation was approved in November 2013, also for 13 years and older, and an IV formulation was approved in March 2014 for patients 18 years and older. Effective absorption of the oral suspension strongly requires taking the medication with food, ideally a high-fat meal; taking posaconazole on an empty stomach will result in approximately one-fourth of the absorption as in the fed state. The tablet formulation has better absorption due to its delayed release in the small intestine, but absorption will still be slightly increased with food. If the patient can take the (relatively large) tablets, the extended-release tablet is the preferred form due to the ability to easily obtain higher and more consistent drug levels. Due to the low pH (<5) of IV posaconazole, a central venous catheter is required for administration. The IV formulation contains only slightly lower amounts of the cyclodextrin vehicle than voriconazole, so similar theoretical renal accumulation concerns exist. The exact pediatric dosing for posaconazole has not been completely determined and requires consultation with a pediatric infectious diseases expert. The pediatric oral suspension dose recommended by some experts for treating invasive disease is 18 mg/kg/day divided 3 times daily. A study with a new pediatric formulation for suspension, essentially the tablet form that is able to be suspended, is underway. Importantly, the current tablet cannot be broken for use due to its chemical coating. The pediatric IV or extended-release tablet dosing is completely unknown, but adolescents can likely follow the adult dosing schemes. In adult patients, IV posaconazole is loaded at 300 mg twice daily on the first day, and then 300 mg once daily starting on the second day. Similarly, in adult patients, the extended-release tablet is dosed as 300 mg twice daily on the first day, and then 300 mg once daily starting on the second day. In adult patients, the maximum amount of posaconazole oral suspension given is 800 mg per day due to its excretion, and that has been given as 400 mg twice daily or 200 mg 4 times a day in severely ill patients due to findings of a marginal increase in exposure with more frequent dosing. Greater than 800 mg per day is not indicated in any patient. Like voriconazole and itraconazole, trough levels should be monitored, and most experts feel that posaconazole levels for treatment should be at least greater than 700 ng/mL (0.7 μg/mL). The in vitro activity of posaconazole against *Candida* spp is better than that of fluconazole and similar to voriconazole. Overall in vitro antifungal activity against *Aspergillus* is also equivalent to voriconazole, but notably it is the first triazole with substantial activity against some *Zygomycetes,* including *Rhizopus* spp and *Mucor* spp, as well as activity against *Coccidioides, Histoplasma,* and *Blastomyces* and the pathogens of phaeohyphomycosis. Posaconazole

treatment of invasive aspergillosis in patients with chronic granulomatous disease appears to be superior to voriconazole in this specific patient population for an unknown reason. Posaconazole is eliminated by hepatic glucuronidation but does demonstrate inhibition of the CYP3A4 enzyme system, leading to many drug interactions with other P450 metabolized drugs. It is currently approved for prophylaxis of *Candida* and *Aspergillus* infections in high-risk adults and for treatment of *Candida* oropharyngeal disease or esophagitis in adults. Posaconazole, like itraconazole, has generally poor CSF penetration.

**Isavuconazole** is a new triazole that was FDA approved in March 2015 for treatment of invasive aspergillosis and invasive mucormycosis with oral (capsules only) and IV formulations. Isavuconazole has a similar antifungal spectrum as voriconazole and some activity against *Zygomycetes* (yet potentially not as potent against *Zygomycetes* as posaconazole). A phase 3 clinical trial in adult patients demonstrated non-inferiority versus voriconazole against invasive aspergillosis and other mold infections. Isavuconazole is actually dispensed as the prodrug isavuconazonium sulfate. Dosing in adults patients is loading with isavuconazole 200 mg (equivalent to 372-mg isavuconazonium sulfate) every 8 hours for 2 days (6 doses), followed by 200 mg once daily for maintenance dosing. The half-life is long (>5 days), there is 98% bioavailability in adults, and there is no reported food effect with oral isavuconazole. The IV formulation does not contain the vehicle cyclodextrin, unlike voriconazole, which could make it more attractive in patients with renal failure. Early experience suggests a much lower rate of photosensitivity and skin disorders as well as visual disturbances compared with voriconazole. No specific pediatric dosing data exist for isavuconazole yet.

## Echinocandins

This class of systemic antifungal agents was first approved in 2001. The echinocandins inhibit cell wall formation (in contrast to acting on the cell membrane by the polyenes and azoles) by noncompetitively inhibiting beta-1,3-glucan synthase, an enzyme present in fungi but absent in mammalian cells. These agents are generally very safe, as there is no beta-1,3-glucan in humans. The echinocandins are not metabolized through the CYP system, so fewer drug interactions are problematic, compared with the azoles. There is no need to dose-adjust in renal failure, but one needs a lower dosage in the setting of very severe hepatic dysfunction. As a class, these antifungals generally have poor CSF penetration, although animal studies have shown adequate brain parenchyma levels, and do not penetrate the urine well. While the 3 clinically available echinocandins each individually have some unique and important dosing and pharmacokinetic parameters, especially in children, efficacy is generally equivalent. Opposite the azole class, the echinocandins are fungicidal against yeasts but fungistatic against molds. The fungicidal activity against yeasts has elevated the echinocandins to the preferred therapy against *Candida* in a neutropenic or critically ill patient. Echinocandins are thought to be best utilized against invasive aspergillosis only as salvage therapy if a triazole fails or in a patient with suspected triazole resistance, but not as primary monotherapy against invasive aspergillosis or any other mold infection. Improved efficacy with combination therapy with the echinocandins and triazoles against *Aspergillus* infections is unclear, with disparate results

in multiple smaller studies and a definitive clinical trial demonstrating minimal benefit over voriconazole monotherapy in certain patient populations. Some experts have used combination therapy in invasive aspergillosis with a triazole plus echinocandin only during the initial phase of waiting for triazole drug levels to be appropriately high. There are reports of echinocandin resistance in *Candida* spp, as high as 12% in *C glabrata* in some studies, and the echinocandins as a class are often somewhat less active against *Candida parapsilosis* isolates (approximately 10%–15% respond poorly, but most are still susceptible).

**Caspofungin** received FDA approval for children aged 3 months to 17 years in 2008 for empiric therapy of presumed fungal infections in febrile, neutropenic children; treatment of candidemia as well as *Candida* esophagitis, peritonitis, and empyema; and salvage therapy of invasive aspergillosis. Due to its earlier approval, there are generally more reports with caspofungin than the other echinocandins. Caspofungin dosing in children is calculated according to body surface area, with a loading dose on the first day of 70 mg/m$^2$, followed by daily maintenance dosing of 50 mg/m$^2$, and not to exceed 70 mg regardless of the calculated dose. Significantly higher doses of caspofungin have been studied in adult patients without any clear added benefit in efficacy, but if the 50 mg/m$^2$ dose is tolerated and does not provide adequate clinical response, the daily dose can be increased to 70 mg/m$^2$. Dosing for caspofungin in neonates is 25 mg/m$^2$/day.

**Micafungin** was approved in adults in 2005 for treatment of candidemia, *Candida* esophagitis and peritonitis, and prophylaxis of *Candida* infections in stem cell transplant recipients, and in 2013 for pediatric patients aged 4 months and older. Micafungin has the most pediatric and neonatal data available of all 3 echinocandins, including more extensive pharmacokinetic studies surrounding dosing and several efficacy studies.[5–7] Micafungin dosing in children is age dependent, as clearance increases dramatically in the younger age groups (especially neonates), necessitating higher doses for younger children. Doses in children are generally thought to be 2 to 4 mg/kg/day, with higher doses likely needed for younger patients, and premature neonates dosed at 10 mg/kg/day. Adult micafungin dosing (100 or 150 mg once daily) is to be used in patients who weigh more than 40 kg. Unlike the other echinocandins, a loading dose is not required for micafungin.

**Anidulafungin** was approved for adults for candidemia and *Candida* esophagitis in 2006 and is not officially approved for pediatric patients. Like the other echinocandins, anidulafungin is not P450 metabolized and has not demonstrated significant drug interactions. Limited clinical efficacy data are available in children, with only some pediatric pharmacokinetic data suggesting weight-based dosing (3 mg/kg/d loading dose, followed by 1.5 mg/kg/d maintenance dosing).[8] The adult dose for invasive candidiasis is a loading dose of 200 mg on the first day, followed by 100 mg daily.

## 3. How Antibiotic Dosages Are Determined Using Susceptibility Data, Pharmacodynamics, and Treatment Outcomes

### Factors Involved in Dosing Recommendations

Our view of how to use antimicrobials is continually changing. As the published literature and our experience with each drug increase, our recommendations evolve as we compare the efficacy, safety, and cost of each drug in the context of current and previous data from adults and children. Every new antibiotic must demonstrate some degree of efficacy and safety in adults before we attempt to treat children. Occasionally, due to unanticipated toxicities and unanticipated clinical failures at a specific dosage, we will modify our initial recommendations.

Important considerations in any new recommendations we make include (1) the susceptibilities of pathogens to antibiotics, which are constantly changing, are different from region to region, and are hospital- and unit-specific; (2) the antibiotic concentrations achieved at the site of infection over a 24-hour dosing interval; (3) the mechanism of how antibiotics kill bacteria; (4) how often the dose we select produces a clinical and microbiological cure; (5) how often we encounter toxicity; and (6) how likely the antibiotic exposure will lead to antibiotic resistance in the treated child and in the population in general.

### Susceptibility

Susceptibility data for each bacterial pathogen against a wide range of antibiotics are available from the microbiology laboratory of virtually every hospital. This antibiogram can help guide you in antibiotic selection for empiric therapy. Many hospitals can separate the inpatient culture results from outpatient results, and many can give you the data by ward of the hospital (eg, pediatric ward vs neonatal intensive care unit vs adult intensive care unit). Susceptibility data are also available by region and by country from reference laboratories or public health laboratories. The recommendations made in *Nelson's Pediatric Antimicrobial Therapy* reflect overall susceptibility patterns present in the United States. Wide variations may exist for certain pathogens in different regions of the United States and the world.

### Drug Concentrations at the Site of Infection

With every antibiotic, we can measure the concentration of antibiotic present in the serum. We can also directly measure the concentrations in specific tissue sites, such as spinal fluid or middle ear fluid. Because free, nonprotein-bound antibiotic is required to inhibit and kill pathogens, it is also important to calculate the amount of free drug available at the site of infection. While traditional methods of measuring antibiotics focused on the peak concentrations in serum and how rapidly the drugs were excreted, complex models of drug distribution and elimination now exist not only for the serum but for other tissue compartments as well. Antibiotic exposure to pathogens at the site of infection can be described in many ways: (1) the percentage of time in a 24-hour dosing interval that the antibiotic concentrations are above the minimum inhibitory concentration (MIC; the antibiotic concentration required for inhibition of growth of an organism)

at the site of infection (%T>MIC); (2) the mathematically calculated area below the serum concentration-versus-time curve (area under the curve [AUC]); and (3) the maximal concentration of drug achieved at the tissue site (Cmax). For each of these 3 values, a ratio of that value to the MIC of the pathogen in question can be calculated and provides more useful information on specific drug activity against a specific pathogen than simply looking at the MIC. It allows us to compare the exposure of different antibiotics (that achieve quite different concentrations in tissues) to a pathogen (where the MIC for each drug may be different) and to assess the activity of a single antibiotic that may be used for empiric therapy against the many different pathogens that may be causing an infection at that tissue site.

## Pharmacodynamics

Pharmacodynamic data provide the clinician with information on how the bacterial pathogens are killed (see Suggested Reading). Beta-lactam antibiotics tend to eradicate bacteria following prolonged exposure of the antibiotic to the pathogen at the site of infection, usually expressed as noted previously, the percent of time over a dosing interval that the antibiotic is present at the site of infection in concentrations greater than the MIC (%T>MIC). For example, amoxicillin needs to be present at the site of pneumococcal infection at a concentration above the MIC for only 40% of a 24-hour dosing interval. Remarkably, neither higher concentrations of amoxicillin nor a more prolonged exposure will substantially increase the cure rate. On the other hand, gentamicin's activity against *Escherichia coli* is based primarily on the absolute concentration of free antibiotic at the site of infection, in the context of the MIC of the pathogen (Cmax:MIC). The more antibiotic you can deliver to the site of infection, the more rapidly you can sterilize the tissue; we are only limited by the toxicities of gentamicin. For fluoroquinolones like ciprofloxacin, the antibiotic exposure best linked to clinical and microbiologic success is the AUC:MIC.

## Assessment of Clinical and Microbiological Outcomes

In clinical trials of anti-infective agents, most adults and children will hopefully be cured, but a few will fail therapy. For those few, we may note inadequate drug exposure (eg, more rapid drug elimination in a particular patient) or infection caused by a pathogen with a particularly high MIC. By analyzing the successes and the failures based on the appropriate exposure parameters outlined previously (%T>MIC, AUC:MIC, or Cmax:MIC), we can often observe a particular value of exposure, above which we observe a higher rate of cure and below which the cure rate drops quickly. Knowing this target value (the "antibiotic exposure break point") allows us to calculate the dosage that will create treatment success in most children. It is this dosage that we subsequently offer to you (if we have it) as one likely to cure your patient. Break points that are reported by microbiology laboratories (S, I, and R) are now determined by outcomes linked to drug exposure, the MIC, and the pharmacodynamic parameter for that agent.

## Suggested Reading

Bradley JS, et al. *Pediatr Infect Dis J.* 2010;29(11):1043–1046 PMID: 20975453

## 4. Community-Associated Methicillin-Resistant *Staphylococcus aureus*

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is a community pathogen for children (that can also spread from child to child in hospitals) that first appeared in the United States in the mid-1990s and currently represents 30% to 80% of all community isolates in various regions of the United States (check your hospital microbiology laboratory for your local rate); it is increasingly present in many areas of the world, with some strain variation documented. This CA-MRSA, like the hospital-associated MRSA strain that has been prevalent for the past 40 years, is resistant to methicillin and to all other beta-lactam antibiotics, except for the newly US Food and Drug Administration (FDA)-approved fifth-generation cephalosporin antibiotic, ceftaroline, for which pediatric data on pharmacokinetics, safety, and efficacy have been submitted for publication. There are an undetermined number of pathogenicity factors that make CA-MRSA more aggressive than methicillin-susceptible *S aureus* (MSSA), which has been a standard pediatric pathogen for decades. Community-associated MRSA seems to cause greater tissue necrosis, an increased host inflammatory response, an increased rate of complications, and an increased rate of recurrent infections compared with MSSA. Response to therapy with non–beta-lactam antibiotics (eg, vancomycin, clindamycin) seems to be inferior compared with the response of MSSA to oxacillin/nafcillin or cefazolin, but it is unknown whether poorer outcomes are due to a hardier, better-adapted, more aggressive CA-MRSA or whether these alternative agents are just not as effective against MRSA as beta-lactam agents are against MSSA. Recent guidelines have been published by the Infectious Diseases Society of America.[1]

### Therapy for CA-MRSA

**Vancomycin (intravenous [IV])** has been the mainstay of parenteral therapy of MRSA infections for the past 4 decades and continues to have activity against more than 98% of strains isolated from children. A few cases of intermediate resistance and "heteroresistance" (transient moderately increased resistance based on thickened staphylococcal cell walls) have been reported, most commonly in adults who are receiving long-term therapy or who have received multiple exposures to vancomycin. Unfortunately, the response to therapy using standard vancomycin dosing of 40 mg/kg/day in the treatment of the new CA-MRSA strains has not been as predictably successful as in the past with MSSA. Increasingly, data in adults suggest that serum trough concentrations of vancomycin in treating serious CA-MRSA infections should be kept in the range of 15 to 20 μg/mL, which frequently causes toxicity in adults. For children, serum trough concentrations of 15 to 20 μg/mL can usually be achieved using the old pediatric "meningitis dosage" of vancomycin of 60 mg/kg/day. Although no prospectively collected data are available, it appears that this dosage in children is reasonably effective and not associated with the degree of nephrotoxicity observed in adults. For vancomycin, the area under the curve to minimum inhibitory concentration (AUC:MIC) ratio that best predicts a successful outcome is about 400 or greater, which is achievable for CA-MRSA strains with in vitro MIC values of 1 μg/mL or less but difficult to achieve for strains with 2 μg/mL or greater.[2] Strains with MIC values of 4 μg/mL or greater should generally be considered resistant to vancomycin. At these higher

"meningitis" treatment dosages, one needs to follow renal function for the development of toxicity.

**Clindamycin (oral [PO] or IV)** is active against approximately 70% to 90% of strains, with great geographic variability (again, check with your hospital laboratory). The dosage for moderate to severe infections is 30 to 40 mg/kg/day, in 3 divided doses, using the same mg/kg dose PO or IV. Clindamycin is not as bactericidal as vancomycin but achieves higher concentrations in abscesses. Some CA-MRSA strains are susceptible to clindamycin on initial testing but have inducible clindamycin resistance (methylase-mediated) that is usually assessed by the "D-test." Within each population of these CA-MRSA organisms, a rare organism will have a mutation that allows for constant (rather than induced) resistance. Although still somewhat controversial, clindamycin should be effective therapy for infections that have a relatively low organism load (cellulitis, small abscesses) and are unlikely to contain a significant population of these mutants. Infections with a high organism load (empyema) may have a greater risk of failure against strains positive on the D-test (as a large population is more likelihood to have a significant number of truly resistant organisms), and clindamycin should not be used as the preferred agent for these strains. Some laboratories no longer report D-test results but simply call the organism "resistant."





Clindamycin is used to treat most CA-MRSA infections that are not life-threatening, and, if the child responds, therapy can be switched from IV to PO (although the oral solution is not very well tolerated). *Clostridium difficile* enterocolitis is a concern as a clindamycin-associated complication; however, despite a great increase in the use of clindamycin in children during the past decade, there are no recent published data on a clinically significant increase in the rate of this complication in children.

**Trimethoprim/sulfamethoxazole (TMP/SMX) (PO, IV),** Bactrim/Septra, is active against CA-MRSA in vitro. New, prospective comparative data on treatment of skin or skin structure infections in adults and children document efficacy equivalent to clindamycin.[3] Given our current lack of prospective, comparative information in MRSA bacteremia, pneumonia, and osteomyelitis (in contrast to skin infections), TMP/SMX should not be used routinely to treat these more serious infections.

**Linezolid, Zyvox (PO, IV),** active against virtually 100% of CA-MRSA strains, is another reasonable alternative but is considered bacteriostatic and has relatively frequent hematologic toxicity in adults (neutropenia, thrombocytopenia) and some infrequent neurologic toxicity (peripheral neuropathy, optic neuritis), particularly when used for courses of 2 weeks or longer (a complete blood cell count should be checked every week or 2 in children receiving prolonged linezolid therapy). It is still under patent at publication time, so the cost is substantially more than clindamycin or vancomycin.

**Daptomycin (IV),** FDA approved for adults for skin infections and bacteremia/endocarditis, is a new class of antibiotic, a lipopeptide, and is highly bactericidal. Daptomycin should be considered for treatment of skin infection and bacteremia in failures with other, better

studied antibiotics. **Daptomycin should not be used to treat pneumonia,** as it is inactivated by pulmonary surfactant. Pediatric studies for skin infections have been completed, and those for bacteremia and osteomyelitis are under way. Some new animal toxicity data suggest additional caution for the use of daptomycin in infants younger than 1 year, prompting a change in the package label. Pediatric clinical trial investigations in these younger infants are not proceeding at this time.

**Tigecycline and fluoroquinolones,** both of which may show in vitro activity, are not generally recommended for children if other agents are available and are tolerated due to potential toxicity issues for children with tetracyclines and fluoroquinolones and rapid emergence of resistance with fluoroquinolones.

**Ceftaroline,** a fifth-generation cephalosporin antibiotic, is the first beta-lactam antibiotic to be active against MRSA. The gram-negative coverage is similar to cefotaxime, with no activity against *Pseudomonas.* As of publication date, pediatric pharmacokinetic data have been collected for all age groups, and studies for skin and skin structure infections and community-acquired pneumonia are completed in children. The efficacy and toxicity profile in adults is what one would expect from most cephalosporins.

**Combination therapy** for serious infections, with vancomycin and rifampin (for deep abscesses) or vancomycin and gentamicin (for bacteremia), is often used, but no prospective, controlled human clinical data exist on improved efficacy over single antibiotic therapy. Some experts use vancomycin and clindamycin in combination, particularly for children with a toxic-shock clinical presentation.

### New Agents Recently Approved for Adults to Be Studied in Children

**Dalbavancin and Oritavancin.** Both antibiotics are IV glycopeptides structurally very similar to vancomycin but with enhanced in vitro activity against MRSA and a much longer serum half-life, allowing once-weekly dosing (dalbavancin) or even just a single dose to treat skin infections.

**Telavancin.** A glyco-lipopeptide with mechanisms of activity that include cell wall inhibition and cell membrane depolarization, telavancin is administered once daily.

**Tedizolid.** A second-generation oxazolidinone like linezolid, tedizolid is more potent in vitro against MRSA than linezolid, with somewhat decreased toxicity to bone marrow in adult clinical studies.

### Life-Threatening and Serious Infections

If any CA-MRSA is present in your community, empiric therapy for presumed staphylococcal infections that are life-threatening or infections for which any risk of failure is unacceptable (eg, meningitis) should follow the recommendations for CA-MRSA and include high-dose vancomycin, clindamycin, or linezolid, in addition to nafcillin or oxacillin (beta-lactam antibiotics are considered better than vancomycin or clindamycin for MSSA).

## Moderate Infections

If you live in a location with greater than 10% methicillin resistance, consider using the CA-MRSA recommendations for hospitalized children with presumed staphylococcal infections of any severity, and start empiric therapy with clindamycin (usually active against >90% of CA-MRSA), vancomycin, or linezolid IV.

In skin and skin structure abscesses, drainage of the abscess may be completely curative in some children, and antibiotics may not be necessary following incision and drainage.

## Mild Infections

For nonserious, presumed staphylococcal infections in regions with significant CA-MRSA, empiric topical therapy with mupirocin (Bactroban) or retapamulin (Altabax) ointment, or oral therapy with TMP/SMX or clindamycin, are preferred. For older children, doxycycline and minocycline are also options based on data in adults.

## Recurrent Infections

For children with problematic, recurrent infections, no well-studied, prospectively collected data provide a solution. Bleach baths (one-half cup of bleach in a full bathtub[4]) seems to be able to transiently decrease the numbers of colonizing organisms but was not shown to decrease the number of infections in a prospective, controlled study of children with eczema. Bathing with chlorhexidine (Hibiclens, a preoperative antibacterial skin disinfectant) daily or a few times each week should provide topical anti-MRSA activity for several hours following a bath, but no prospective data exist yet to document benefit. Nasal mupirocin ointment (Bactroban) designed to eradicate colonization may also be used. All of these measures have advantages and disadvantages and need to be used together with environment measures (eg, washing towels frequently, using hand sanitizers, not sharing items of clothing). Helpful advice can be found on the Centers for Disease Control and Prevention Web site at www.cdc.gov/mrsa.

## 5. Antimicrobial Therapy for Newborns

### NOTES

- Prospectively collected data in newborns continue to become available, thanks in large part to federal legislation (including the US Food and Drug Administration [FDA] Safety and Innovation Act of 2012 that mandates neonatal studies). In situations of inadequate data, suggested doses are based on efficacy, safety, and pharmacologic data from older children or adults. These may not account for the effect of developmental changes (effect of ontogeny) on drug metabolism that occur during early infancy and among premature and full-term newborns.[1] These values may vary widely, particularly for the unstable premature newborn. Oral convalescent therapy for neonatal infections has not been well studied but may be used cautiously in non–life-threatening infections in adherent families with ready access to medical care.[2]
- The recommended antibiotic dosages and intervals of administration are given in the tables at the end of this chapter.
- **Adverse drug reaction:** Neonates should not receive intravenous (IV) ceftriaxone while receiving IV calcium-containing products, including parenteral nutrition, by the same or different infusion lines, as fatal reactions with ceftriaxone-calcium precipitates in lungs and kidneys in neonates have occurred. There are no data on interactions between IV ceftriaxone and oral calcium-containing products or between intramuscular ceftriaxone and IV or oral calcium-containing products. Current information is available on the FDA Web site.[3] Cefotaxime is preferred over ceftriaxone for neonates.[4]
- **Abbreviations:** 3TC, lamivudine; ABLC, lipid complex amphotericin; ABR, auditory brainstem response; ALT, alanine transaminase; AmB, amphotericin B; AmB-D, AmB deoxycholate; amox/clav, amoxicillin/clavulanate; AOM, acute otitis media; AST, aspartate transaminase; bid, twice daily; CBC, complete blood cell count; CLD, chronic lung disease; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; div, divided; echo, echocardiogram; ECMO, extracorporeal membrane oxygenation; ESBL, extended spectrum beta-lactamase; FDA, US Food and Drug Administration; GA, gestational age; GBS, group B streptococcus; G-CSF, granulocyte colony stimulating factor; HIV, human immunodeficiency virus; HSV, herpes simplex virus; ID, infectious diseases; IM, intramuscular; IUGR, intrauterine growth retardation; IV, intravenous; IVIG, intravenous immune globulin; L-AmB, liposomal AmB; MRSA, methicillin-resistant *Staphylococcus aureus;* MSSA, methicillin-susceptible *S aureus;* NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NVP, nevirapine; PCR, polymerase chain reaction; pip/tazo, piperacillin/tazobactam; PO, orally; RSV, respiratory syncytial virus; spp, species; ticar/clav, ticarcillin/clavulanate; tid, 3 times daily; TIG, tetanus immune globulin; TMP/SMX, trimethoprim/sulfamethoxazole; UTI, urinary tract infection; VCUG, voiding cystourethrogram; VDRL, Venereal Disease Research Laboratories; ZDV, zidovudine.

## A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS

| Condition | Therapy (evidence grade)<br>*See Tables 5B–D for neonatal dosages.* | Comments |
|---|---|---|
| **Conjunctivitis** | | |
| – Chlamydial[5–8] | Azithromycin 10 mg/kg/day PO for 1 day, then 5 mg/kg/day PO for 4 days (AII), or erythromycin ethylsuccinate PO for 10–14 days (AII) | Macrolides PO preferred to topical eyedrops to prevent development of pneumonia; association of erythromycin and pyloric stenosis in young neonates.[9]<br>Alternative: 3-day course of higher-dose azithromycin at 10 mg/kg/dose once daily, although safety not well defined in neonates (CIII).<br>Oral sulfonamides may be used after the immediate neonatal period for infants who do not tolerate erythromycin. |
| – Gonococcal[10–14] | Ceftriaxone 25–50 mg/kg (max 125 mg) IV, IM once, AND azithromycin 10 mg/kg PO q24h for 5 days (AIII) | Ceftriaxone no longer recommended as single agent therapy due to increasing cephalosporin resistance; therefore, addition of azithromycin recommended (no data in neonates; azithromycin dose is that recommended for pertussis). Cefotaxime is preferred for neonates with hyperbilirubinemia.<br>Saline irrigation of eyes.<br>Evaluate for chlamydial infection.<br>All neonates born to mothers with untreated gonococcal infection (regardless of symptoms) require therapy. Cefixime and ciprofloxacin no longer recommended for empiric maternal therapy. |
| – *Staphylococcus aureus*[15–17] | Topical therapy sufficient for mild *S aureus* cases (AII), but oral or IV therapy may be considered for moderate to severe conjunctivitis.<br>MSSA: oxacillin/nafcillin IV or cefazolin (for non-CNS infections) IM, IV for 7 days.<br>MRSA: vancomycin IV or clindamycin IV, PO. | Neomycin or erythromycin (BIII) ophthalmic drops or ointment<br>No prospective data for MRSA conjunctivitis (BIII)<br>Cephalexin PO for mild-moderate disease caused by MSSA<br>Increased *S aureus* resistance with ciprofloxacin/levofloxacin ophthalmic formulations (AII) |
| – *Pseudomonas aeruginosa*[18–20] | Ceftazidime IM, IV AND tobramycin IM, IV for 7–10 days (alternatives: meropenem, cefepime, pip/tazo) (BIII) | Aminoglycoside or polymyxin B–containing ophthalmic drops or ointment as adjunctive therapy |

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| – Other gram-negative | Aminoglycoside or polymyxin B–containing ophthalmic drops or ointment if mild (AII)<br>Systemic therapy if moderate to severe or unresponsive to topical therapy (AIII) | Duration of therapy dependent on clinical course and may be as short as 5 days if clinically resolved. |
| **Cytomegalovirus** | | |
| – Congenital[21–24] | For moderately to severely symptomatic neonates with congenital infection syndrome and multisystem disease: oral valganciclovir at 16 mg/kg/dose PO bid for 6 mo[24] (AI); IV ganciclovir 6 mg/kg/dose IV q12h can be used for some or all of the first 6 wk of therapy if oral therapy not advised (AII). | Benefit for hearing loss and neurodevelopmental outcomes (AI).<br>Treatment recommended for neonates with moderate or severe symptomatic congenital CMV disease, with or without CNS involvement.<br>Treatment of "mildly symptomatic" (only 1 or perhaps 2 manifestations of congenital CMV infection, which are mild in scope [eg, slight IUGR, mild hepatomegaly] or transient and mild in nature [eg, a single platelet count of 80,000 or an ALT of 130]) neonates congenitally infected with CMV is not routinely recommended, as the risks of treatment may not be balanced by benefits in mild disease that is often reversible without long-term sequelae.[25] This includes neonates who are asymptomatic except for sensorineural hearing loss.<br>Treatment for asymptomatic neonates congenitally infected with CMV is not recommended.<br>Neutropenia in 20% (oral valganciclovir) to 68% (IV ganciclovir) of neonates on long-term therapy (responds to G-CSF or temporary discontinuation of therapy).<br>Treatment for congenital CMV should start within the first month of life.<br>CMV-IVIG not recommended. |
| – Perinatally or postnatally acquired[23] | Ganciclovir 12 mg/kg/day IV div q12h for 14–21 days (AIII) | Antiviral treatment has not been studied in this population but can be considered in patients with acute, severe, visceral (end-organ) disease such as pneumonia, hepatitis, encephalitis, necrotizing enterocolitis, or persistent thrombocytopenia. If such patients are treated with parenteral ganciclovir, a reasonable approach is to treat for 2 wk and then reassess responsiveness to therapy. If clinical data suggest benefit of treatment, an additional 1 wk of parenteral ganciclovir can be considered if symptoms and signs have not fully resolved. Observe for possible relapse after completion of therapy (AIII). |

## A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

| Condition | Therapy (evidence grade)<br>*See Tables 5B–D for neonatal dosages.* | Comments |
|---|---|---|
| **Fungal infections (See Chapter 8.)** | | |
| – Candidiasis[26–34] | **Treatment**<br>L-AmB/ABLC (5 mg/kg/day) or AmB-D (1 mg/kg/day).<br>For susceptible strains, fluconazole is usually effective. For treatment of neonates, load with 25 mg/day for day 1, then continue with 12 mg/kg/day (BI).[35]<br>For treatment of neonates and children on ECMO, fluconazole load with 35 mg/kg on day 1, followed by 12 mg/kg/day (BII).[36]<br><br>**Prophylaxis**<br>Fluconazole 6 mg/kg/day twice a week in high-risk neonates (birth weight <1,000 g) in centers where incidence of disease is high (generally thought to be >10%).<br>Neonates and children on ECMO, fluconazole 12 mg/kg on day 1, followed by 6 mg/kg/day (BII). | Prompt removal of all catheters is absolutely essential (AII).<br>Evaluate for other sites of infection: CSF analysis, cardiac echo, abdominal ultrasound to include bladder; retinal eye examination.<br>Length of therapy dependent on disease (BIII), usually 3 wk.<br>Persistent disease requires evaluation of catheter removal or search for disseminated sites. Antifungal susceptibility testing is suggested with persistent disease. (*Candida krusei* inherently resistant to fluconazole; *Candida parapsilosis* may be less susceptible to echinocandins; *Candida glabrata* demonstrates increasing resistance to fluconazole and echinocandins.)<br>No proven benefit for combination antifungal therapy in candidiasis. Change from AmB or fluconazole to micafungin/caspofungin if cultures persistently positive (BIII).<br>Although fluconazole prophylaxis has been shown to reduce colonization, it has not reduced mortality.[29]<br>Role of flucytosine (5-FC) orally in neonates with *Candida* meningitis is not well defined and not routinely recommended due to toxicity concerns.<br>Limited data in humans exist on echinocandin CSF/brain penetration. Animal studies suggest adequate penetration, but clinical utility in the CSF/brain is unclear.<br>Higher echinocandin doses needed in the smallest infants.<br>Fluconazole loading dose is critical to rapidly reach therapeutic concentrations.<br>Antifungal bladder washes not indicated. |

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| – Aspergillosis (usually cutaneous infection with systemic dissemination)[37–39] | Voriconazole (18 mg/kg/day div q12h load, then continue with 16 mg/kg/day; very important to maintain trough serum concentrations ≥2 μg/mL). Duration depends on severity of disease and success of local debridement (BIII). | Aggressive antifungal therapy, early debridement of skin lesions (AIII).<br>Goal serum trough levels are between 2 and 6 μg/mL. Trough levels should be obtained before sixth dose and then intermittently to ensure adequate levels.<br>Not well studied in neonates, but based on experience, neonates will likely require higher doses than older children to achieve adequate trough levels.<br>No significant experience with posaconazole or isavuconazole in neonates. |
| **Gastrointestinal infections** | | |
| – NEC or peritonitis secondary to bowel rupture[40–45] | Ampicillin IV AND gentamicin IM, IV for ≥10 days (AII).<br>Alternatives: pip/tazo AND gentamicin (AII); ceftazidime/cefotaxime AND gentamicin ± metronidazole (BIII); OR meropenem (BI).<br>ADD fluconazole if known to have gastrointestinal colonization with *Candida* (BIII). | Surgical drainage (AII).<br>Definitive antibiotic therapy based on culture results (aerobic, anaerobic, and fungal); meropenem or cefepime if ceftazidime-resistant gram-negative bacilli isolated. Vancomycin rather than ampicillin if MRSA prevalent. *Bacteroides* colonization may occur as early as the first week of life (AIII).[45]<br>Duration of therapy dependent on clinical response and risk of persisting intra-abdominal abscess (AIII).<br>Probiotics may prevent NEC in neonates born <1,500 g, but agent, dose, and safety not fully known.[42,46] |
| – *Salmonella*[47] | Ampicillin IM, IV (if susceptible) OR cefotaxime IM, IV for 7–10 days (AII) | Observe for focal complications (eg, meningitis, arthritis) (AIII). |
| **Herpes simplex infection** | | |
| – CNS and disseminated disease[48–50] | Acyclovir IV for 21 days (AII) (If eye disease present, ADD topical 1% trifluridine or 0.15% ganciclovir ophthalmic gel.) (AII) | For CNS disease, perform CSF HSV PCR near end of 21 days of therapy and continue acyclovir until PCR negative.<br>Serum AST/ALT may help identify early disseminated infection.<br>Foscarnet for acyclovir-resistant disease.<br>Acyclovir PO (300 mg/m$^2$/dose tid) suppression for 6 mo recommended following parenteral therapy (AI).[51]<br>Monitor for neutropenia during suppressive therapy.<br>Different dosages than those listed in Table 5B have been modeled, but there are no safety or efficacy data in humans to support them.[52] |

## A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

| Condition | Therapy (evidence grade)<br>*See Tables 5B–D for neonatal dosages.* | Comments |
|---|---|---|
| – Skin, eye, or mouth disease[48–50] | Acyclovir IV for 14 days (AII) (if eye disease present, ADD topical 1% trifluridine or 0.15% ganciclovir ophthalmic gel) (AII).<br>Obtain CSF PCR for HSV to assess for CNS infection. | Acyclovir PO (300 mg/m$^2$/dose tid) suppression for 6 mo recommended following parenteral therapy (AI).[51]<br>Monitor for neutropenia during suppressive therapy.<br>Different dosages than those listed in Table 5B have been modeled, but there are no safety or efficacy data in humans to support them.[52] |
| **Human immunodeficiency virus infection**[53,54] | There has been recent interest in using "treatment" antiretroviral regimens for high-risk, exposed neonates in an attempt to achieve a remission or possibly even a cure. This was initially stimulated by the experience of a baby from Mississippi: high-risk neonate treated within the first 2 days of life with subsequent infection documentation; off therapy at 18 mo of age without evidence of circulating virus until 4 y of age, at which point HIV became detectable. While a clinical trial is ongoing to study issues further, full treatment dosing of high-risk neonates is not currently recommended due to lack of safety and dosing data and lack of defined efficacy. | |
| | Peripartum presumptive preventive therapy for HIV-exposed newborns: ZDV for the first 6 wk of age (AI).<br>GA ≥35 wk: ZDV 8 mg/kg/day PO div bid OR 6 mg/kg/day IV div q8h for 6 wk.<br>GA <35 wk but >30 wk: ZDV 4 mg/kg/day PO (OR 3 mg/kg/day IV) div q12h. Increase at 2 wk of age to 6 mg/kg/day PO (OR 4.6 mg/kg/day IV) div q12h.<br>GA ≤30 wk: ZDV 4 mg/kg/day PO (OR 3 mg/kg/day IV) div q12h. Increase at 4 wk of age to 6 mg/kg/day PO (OR 4.6 mg/kg/day IV) div q12h.<br>For newborns whose mothers received NO antenatal antiretroviral therapy, add 3 doses of NVP (first dose at 0–48 h; second dose 48 h later; third dose 96 h after second dose) to the 6 wk of ZDV treatment (AI). | For detailed information: http://aidsinfo.nih.gov/Guidelines (accessed August 27, 2015).<br>National Perinatal HIV Consultation and Referral Service (888/448-8765) provides free clinical consultation.<br>Start therapy at 6–8 h of age if possible (AII).<br>Monitor CBC at birth and 4 wk (AII).<br>Some experts consider the use of ZDV in combination with other antiretroviral drugs in certain situations (eg, mothers with minimal intervention before delivery, have high viral load, with known resistant virus). Consultation with a pediatric HIV specialist is recommended (BIII).<br>Perform HIV-1 DNA PCR or RNA assays at 14–21 days, 1–2 mo, and 4–6 mo (AI).<br>Initiate prophylaxis for pneumocystis pneumonia at 6 wk of age if HIV infection not yet excluded (AII). |

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| | NVP dose: birth weight 1.5–2 kg: 8 mg/dose PO; birth weight >2 kg: 12 mg/dose PO (AI).[55]<br>The preventive ZDV doses listed above for neonates are also treatment doses for infants with diagnosed HIV infection. Note that antiretroviral treatment doses for neonates are established only for ZDV and 3TC (4 mg/kg/day div q12h). Treatment of HIV-infected neonates should be considered only with expert consultation. | |
| **Influenza A and B viruses**[56–59] | Preterm, <38 wk postmenstrual age: 1 mg/kg/dose PO bid<br>Preterm, 38–40 wk postmenstrual age: 1.5 mg/kg/dose PO bid<br>Preterm, >40 wk postmenstrual age: 3 mg/kg/dose PO bid[57]<br>Term, birth–8 mo: 3 mg/kg/dose PO bid[57,60] | Oseltamivir chemoprophylaxis not recommended for infants <3 mo unless the situation is judged critical because of limited safety and efficacy data in this age group. |
| **Omphalitis and funisitis** | | |
| – Empiric therapy for omphalitis and necrotizing funisitis direct therapy against coliform bacilli, *S aureus* (consider MRSA), and anaerobes[61–63] | Cefotaxime OR gentamicin, AND clindamycin for ≥10 days (AII) | Need to culture to direct therapy.<br>Alternatives for coliform coverage if resistance likely: cefepime, meropenem.<br>For suspect MRSA: add vancomycin.<br>Alternatives for combined MSSA and anaerobic coverage: pip/tazo or ticar/clav.<br>Appropriate wound management for infected cord and necrotic tissue (AIII). |
| – Group A or B streptococci[64] | Penicillin G IV for ≥7–14 days (shorter course for superficial funisitis without invasive infection) (AII) | Group A streptococcus usually causes "wet cord" without pus and with minimal erythema; single dose of benzathine penicillin IM adequate.<br>Consultation with pediatric ID specialist is recommended for necrotizing fasciitis (AII). |

## A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

| Condition | Therapy (evidence grade)<br>*See Tables 5B–D for neonatal dosages.* | Comments |
|---|---|---|
| – *S aureus*[63] | MSSA: oxacillin/nafcillin IV, IM for ≥5–7 days (shorter course for superficial funisitis without invasive infection) (AIII)<br>MRSA: vancomycin (AIII) | Assess for bacteremia and other focus of infection.<br>Alternatives for MRSA: linezolid, clindamycin (if susceptible). |
| – *Clostridium* spp[65] | Clindamycin OR penicillin G IV for ≥10 days, with additional agents based on culture results (AII) | Crepitance and rapidly spreading cellulitis around umbilicus<br>Mixed infection with other gram-positive and gram-negative bacteria common |
| **Osteomyelitis, suppurative arthritis**[66–68]<br>Obtain cultures (aerobic; fungal if NICU) of bone or joint fluid before antibiotic therapy.<br>Duration of therapy dependent on causative organism and normalization of erythrocyte sedimentation rate and C-reactive protein; minimum for osteomyelitis 3 wk and arthritis therapy 2–3 wk if no organism identified (AIII).<br>Surgical drainage of pus (AIII); physical therapy may be needed (BIII). | | |
| – Empiric therapy | Nafcillin/oxacillin IV (or vancomycin if MRSA is a concern) AND cefotaxime or gentamicin IV, IM (AIII) | |
| – Coliform bacteria (eg, *Escherichia coli, Klebsiella* spp, *Enterobacter* spp) | For *E coli* and *Klebsiella:* cefotaxime OR gentamicin OR ampicillin (if susceptible) (AIII).<br>For *Enterobacter, Serratia,* or *Citrobacter:* ADD gentamicin IV, IM to cefotaxime or ceftriaxone, OR use cefepime or meropenem alone (AIII). | Meropenem for ESBL-producing coliforms (AIII).<br>Pip/tazo or cefepime are alternatives for susceptible bacilli (BIII). |
| – Gonococcal arthritis and tenosynovitis[11–14] | Ceftriaxone IV, IM OR cefotaxime IV AND azithromycin 10 mg/kg PO q24h for 5 days (AIII) | Ceftriaxone no longer recommended as single agent therapy due to increasing cephalosporin resistance; therefore, addition of azithromycin recommended (no data in neonates; azithromycin dose is that recommended for pertussis). Cefotaxime is preferred for neonates with hyperbilirubinemia. |

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|---|---|---|
| – *S aureus* | MSSA: oxacillin/nafcillin IV (AII)<br>MRSA: vancomycin IV (AIII) | Alternative for MSSA: cefazolin (AIII)<br>Alternatives for MRSA: linezolid, clindamycin (if susceptible) (BIII)<br>Addition of rifampin if persistently positive cultures |
| – Group B streptococcus | Ampicillin or penicillin G IV (AII) | |
| – *Haemophilus influenzae* | Ampicillin IV OR cefotaxime IV, IM if ampicillin-resistant | Start with IV therapy and switch to oral therapy when clinically stable.<br>Amox/clav PO OR amoxicillin PO if susceptible (AIII). |
| **Otitis media**[69] | No controlled treatment trials in newborns; if no response, obtain middle ear fluid for culture. | In addition to *Pneumococcus* and *Haemophilus,* coliforms and *S aureus* may also cause AOM in neonates (AIII). |
| – Empiric therapy[70] | Oxacillin/nafcillin AND cefotaxime or gentamicin | Start with IV therapy and switch to oral therapy when clinically stable.<br>Amox/clav (AIII). |
| – *E coli* (therapy of other coliforms based on susceptibility testing) | Cefotaxime OR gentamicin | Start with IV therapy and switch to oral therapy when clinically stable.<br>For ESBL-producing strains, use meropenem (AII).<br>Amox/clav if susceptible (AIII). |
| – *S aureus* | MSSA: oxacillin/nafcillin IV<br>MRSA: vancomycin or clindamycin IV (If susceptible) | Start with IV therapy and switch to oral therapy when clinically stable.<br>MSSA: cephalexin PO for 10 days or cloxacillin PO (AIII).<br>MRSA: linezolid PO or clindamycin PO (BIII). |
| – Group A or B streptococcus | Penicillin G or ampicillin IV, IM | Start with IV therapy and switch to oral therapy when clinically stable.<br>Amoxicillin 30–40 mg/kg/day PO div q8h for 10 days. |
| **Parotitis, suppurative**[71] | Oxacillin/nafcillin IV AND gentamicin IV, IM for 10 days; consider vancomycin if MRSA suspected (AIII). | Usually staphylococcal but occasionally coliform.<br>Antimicrobial regimen without incision/drainage is adequate in >75% of cases. |
| **Pulmonary infections** | | |
| – Empiric therapy of the neonate with early onset of pulmonary infiltrates (within the first 48–72 h of life) | Ampicillin IV/IM AND gentamicin or cefotaxime IV/IM for 10 days; many neonatologists treat low-risk neonates for ≤7 days (see Comments). | For newborns with no additional risk factors for bacterial infection (eg, maternal chorioamnionitis) who (1) have negative blood cultures, (2) have no need for >8 h of oxygen, and (3) are asymptomatic at 48 h into therapy, 4 days may be sufficient therapy, based on limited data.[72] |

## A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

| Condition | Therapy (evidence grade)<br>*See Tables 5B–D for neonatal dosages.* | Comments |
|---|---|---|
| – Aspiration pneumonia[73] | Ampicillin IV, IM AND gentamicin IV, IM for 7–10 days (AIII) | Early onset neonatal pneumonia may represent aspiration of amniotic fluid, particularly if fluid is not sterile.<br>Mild aspiration episodes may not require antibiotic therapy. |
| – *Chlamydia trachomatis*[74] | Azithromycin PO, IV q24h for 5 days OR erythromycin ethylsuccinate PO for 14 days (AII) | Association of erythromycin and pyloric stenosis in young infants |
| – *Mycoplasma hominis*[75,76] | Clindamycin PO, IV for 10 days (Organisms are resistant to macrolides.) | Pathogenic role in pneumonia not well defined and clinical efficacy unknown; no association with bronchopulmonary dysplasia (BIII) |
| – Pertussis[77] | Azithromycin 10 mg/kg PO, IV q24h for 5 days OR erythromycin ethylsuccinate PO for 14 days (AII) | Association of erythromycin and pyloric stenosis in young infants; may also occur with azithromycin.<br>Alternatives for >1 mo of age, clarithromycin for 7 days, and for >2 mo of age, TMP/SMX for 14 days. |
| – *P aeruginosa*[78] | Ceftazidime IV, IM AND tobramycin IV, IM for 10–14 days (AIII) | Alternatives: cefepime or meropenem, OR pip/tazo AND tobramycin |
| – Respiratory syncytial virus[79] | Treatment: see Comments.<br>Prophylaxis: palivizumab (Synagis, a monoclonal antibody) 15 mg/kg IM monthly (maximum: 5 doses) for these high-risk infants (AI).<br>In first y of life, palivizumab prophylaxis is recommended for infants born before 29 wk, 0 days' gestation.<br>Palivizumab prophylaxis is not recommended for otherwise healthy infants born at ≥29 wk, 0 days' gestation. | Aerosol ribavirin (6-g vial to make 20-mg/mL solution in sterile water), aerosolized over 18–20 h daily for 3–5 days (BII), provides little benefit and should only be used for life-threatening infection with RSV. Difficulties in administration, complications with airway reactivity, and concern for potential toxicities to health care workers preclude routine use.<br>Palivizumab does not provide benefit in the treatment of an active RSV infection.<br>Palivizumab prophylaxis may be considered for children <24 mo who will be profoundly immunocompromised during the RSV season. |

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| | In first y of life, palivizumab prophylaxis is recommended for preterm infants with CLD of prematurity, defined as birth at <32 wk, 0 days' gestation and a requirement for >21% oxygen for at least 28 days after birth.<br>Clinicians may administer palivizumab prophylaxis in the first year of life to certain infants with hemodynamically significant heart disease. | Palivizumab prophylaxis is not recommended in the second y of life except for children who required at least 28 days of supplemental oxygen after birth and who continue to require medical support (supplemental oxygen, chronic corticosteroid therapy, or diuretic therapy) during the 6-mo period before the start of the second RSV season.<br>Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.<br>Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways may be considered for prophylaxis in the first y of life.<br>Insufficient data are available to recommend palivizumab prophylaxis for children with cystic fibrosis or Down syndrome.<br>The burden of RSV disease and costs associated with transport from remote locations may result in a broader use of palivizumab for RSV prevention in Alaska Native populations and possibly in selected other American Indian populations.<br>Palivizumab prophylaxis is not recommended for prevention of health care–associated RSV disease. |
| – *S aureus*[17,80–82] | MSSA: oxacillin/nafcillin IV (AIII).<br>MRSA: vancomycin IV OR clindamycin IV if susceptible (AIII).<br>Duration of therapy depends on extent of disease (pneumonia vs pulmonary abscesses vs empyema) and should be individualized with therapy up to 21 days or greater. | Alternative for MSSA: cefazolin IV<br>Addition of rifampin or linezolid if persistently positive cultures (AIII)<br>Thoracostomy drainage of empyema |
| – Group B streptococcus[83,84] | Penicillin G IV OR ampicillin IV, IM for 10 days (AIII) | For serious infections, ADD gentamicin for synergy until clinically improved.<br>No prospective, randomized data on the efficacy of a 7-day treatment course. |

## A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

| Condition | Therapy (evidence grade)<br>*See Tables 5B–D for neonatal dosages.* | Comments |
|---|---|---|
| – *Ureaplasma* spp (*urealyticum* or *parvum*)[85] | Azithromycin PO/IV for 5 days or clarithromycin PO for 10 days (BIII) | Pathogenic role of *Ureaplasma* not well defined and no prophylaxis recommended for CLD<br>Many *Ureaplasma* spp resistant to erythromycin<br>Association of erythromycin and pyloric stenosis in young infants |
| **Sepsis and meningitis**[82,86,87] | **NOTE:** Duration of therapy: 10 days for sepsis without a focus (AIII); minimum of 21 days for gram-negative meningitis (or at least 14 days after CSF is sterile) and 14–21 days for GBS meningitis and other gram-positive bacteria (AIII) | There are no prospective, controlled studies on 5- or 7-day courses for mild or presumed sepsis. |
| – Initial therapy, organism unknown | Ampicillin IV AND a second agent, either cefotaxime IV or gentamicin IV, IM (AII) | Cefotaxime preferred if meningitis suspected or cannot be excluded clinically or by lumbar puncture (AIII). For locations with a high rate (10% or greater) of ESBL-producing *E coli,* and meningitis is suspected, empiric therapy with meropenem (or cefepime) is preferred over cefotaxime.<br>For empiric therapy of sepsis without meningitis, in areas with a high rate of ESBL *E coli,* gentamicin is preferred.<br>Initial empiric therapy of nosocomial infection should be based on each hospital's pathogens and susceptibilities.<br>Always narrow antibiotic coverage once susceptibility data are available. |
| – *Bacteroides fragilis* | Metronidazole or meropenem IV, IM (AIII) | Alternative: clindamycin, but increasing resistance reported |
| – *Enterococcus* spp | Ampicillin IV, IM AND gentamicin IV, IM (AIII); for ampicillin-resistant organisms: vancomycin AND gentamicin (AIII) | Gentamicin needed with ampicillin or vancomycin for bactericidal activity; continue until clinical and microbiological response documented (AIII).<br>For vancomycin-resistant enterococci that are also ampicillin resistant: linezolid (AIII). |

| | | |
|---|---|---|
| – *E coli*[86,87] | Cefotaxime IV or gentamicin IV, IM (AII) | Cefotaxime preferred if meningitis suspected or cannot be excluded clinically or by lumbar puncture (AIII).<br>For locations with a high rate (10% or greater) of ESBL-producing *E coli,* and meningitis is suspected, empiric therapy with meropenem (or cefepime) is preferred over cefotaxime. |
| – Gonococcal[11–14] | Ceftriaxone IV, IM OR cefotaxime IV, IM, AND azithromycin 10 mg/kg PO q24h for 5 days (AIII) | Ceftriaxone no longer recommended as single agent therapy due to increasing cephalosporin resistance; therefore, addition of azithromycin recommended (no data in neonates; azithromycin dose is that recommended for pertussis). Cefotaxime is preferred for neonates with hyperbilirubinemia. |
| – *Listeria monocytogenes*[88] | Ampicillin IV, IM AND gentamicin IV, IM (AIII) | Gentamicin is synergistic in vitro with ampicillin. Continue until clinical and microbiological response documented (AIII). |
| – *P aeruginosa* | Ceftazidime IV, IM AND tobramycin IV, IM (AIII) | Meropenem, cefepime, and tobramycin are suitable alternatives (AIII). Pip/tazo should not be used for CNS infection. |
| – *S aureus*[17,80–82,89,90] | MSSA: oxacillin/nafcillin IV, IM or cefazolin IV, IM (AII)<br>MRSA: vancomycin IV (AIII) | Alternatives for MRSA: clindamycin, linezolid |
| – *Staphylococcus epidermidis* (or any coagulase-negative staphylococci) | Vancomycin IV (AIII) | If organism susceptible and infection not severe, oxacillin/nafcillin or cefazolin are alternatives for methicillin-susceptible strains. Cefazolin does not enter CNS.<br>Add rifampin if cultures persistently positive.[91]<br>Alternative: linezolid. |
| – Group A streptococcus | Penicillin G or ampicillin IV (AII) | |
| – Group B streptococcus[83] | Ampicillin or penicillin G IV AND gentamicin IV, IM (AI) | Continue gentamicin until clinical and microbiological response documented (AIII).<br>Duration of therapy: 10 days for bacteremia/sepsis (AII); minimum of 14 days for meningitis (AII). |

## A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

| Condition | Therapy (evidence grade)<br>*See Tables 5B–D for neonatal dosages.* | Comments |
|---|---|---|
| **Skin and soft tissues** | | |
| – Breast abscess[92] | Vancomycin IV (for MRSA) or oxacillin/nafcillin IV, IM (MSSA) AND cefotaxime OR gentamicin if gram-negative rods seen on Gram stain (AIII) | Gram stain of expressed pus guides empiric therapy; vancomycin if MRSA prevalent in community; alternative to vancomycin: clindamycin, linezolid, may need surgical drainage to minimize damage to breast tissue.<br>Treatment duration individualized until clinical findings have completely resolved (AIII). |
| – Erysipelas (and other group A streptococcal infections) | Penicillin G IV for 5–7 days, followed by oral therapy (if bacteremia not present) to complete a 10-day course (AIII) | Alternative: ampicillin.<br>GBS may produce similar cellulitis or nodular lesions. |
| – Impetigo neonatorum | MSSA: oxacillin/nafcillin IV, IM OR cephalexin (AIII)<br>MRSA: vancomycin IV for 5 days (AIII) | Systemic antibiotic therapy usually not required for superficial impetigo; local chlorhexidine cleansing may help with or without topical mupirocin (MRSA) or bacitracin (MSSA).<br>Alternatives for MRSA: clindamycin IV, PO or linezolid IV, PO. |
| – *S aureus*[17,80,82,93] | MSSA: oxacillin/nafcillin IV, IM (AII)<br>MRSA: vancomycin IV (AIII) | Surgical drainage may be required.<br>MRSA may cause necrotizing fasciitis.<br>Alternatives for MRSA: clindamycin IV or linezolid IV.<br>Convalescent oral therapy if infection responds quickly to IV therapy. |
| – Group B streptococcus[83] | Penicillin G IV OR ampicillin IV, IM | Usually no pus formed<br>Treatment course dependent on extent of infection, 7–14 days |
| **Syphilis, congenital (<1 mo of age)**[94] | During periods when availability of penicillin is compromised, see www.cdc.gov/std/Treatment/misc/penicillinG.htm. | Evaluation and treatment do not depend on mother's HIV status.<br>Obtain follow-up serology every 2–3 mo until nontreponemal test nonreactive or decreased 4-fold.<br>If CSF positive, repeat spinal tap with CSF VDRL at 6 mo, and if abnormal, re-treat. |

| | | |
|---|---|---|
| – Proven or highly probable disease:<br>(1) abnormal physical examination;<br>(2) serum quantitative nontreponemal serologic titer 4-fold higher than mother's titer; or (3) positive dark field or fluorescent antibody test of body fluid(s) | Aqueous penicillin G 50,000 U/kg/dose q12h (day of life 1–7), q8h (>7 days) IV OR procaine penicillin G 50,000 U/kg IM q24h for 10 days (AII) | Evaluation to determine type and duration of therapy: CSF analysis (VDRL, cell count, protein), CBC and platelet count. Other tests as clinically indicated, including long-bone radiographs, chest radiograph, liver function tests, cranial ultrasound, ophthalmologic examination, and hearing test (ABR).<br>If >1 day of therapy is missed, entire course is restarted. |
| – Normal physical examination, serum quantitative nontreponemal serologic titer ≤maternal titer, and maternal treatment was (1) none, inadequate, or undocumented; (2) erythromycin, azithromycin, or other non-penicillin regimen; or (3) <4 wk before delivery | Evaluation abnormal or not done completely: aqueous penicillin G 50,000 U/kg/dose q12h (day of life 1–7), q8h (>7 days) IV OR procaine penicillin G 50,000 U/kg IM q24h for 10 days (AII)<br>Evaluation normal: aqueous penicillin G 50,000 U/kg/dose q12h (day of life 1–7), q8h (>7 days) IV OR procaine penicillin G 50,000 U/kg IM q24h for 10 days; OR benzathine penicillin G 50,000 units/kg/dose IM in a single dose (AIII) | Evaluation: CSF analysis, CBC with platelets, long-bone radiographs.<br>If >1 day of therapy is missed, entire course is restarted.<br>Reliable follow-up important if only a single dose of benzathine penicillin given. |

## A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

| Condition | Therapy (evidence grade)<br>*See Tables 5B–D for neonatal dosages.* | Comments |
|---|---|---|
| – Normal physical examination, serum quantitative nontreponemal serologic titer ≤maternal titer, mother treated adequately during pregnancy and >4 wk before delivery; no evidence of reinfection or relapse in mother | Benzathine penicillin G 50,000 units/kg/dose IM in a single dose (AIII) | No evaluation required.<br>Some experts would not treat but provide close serologic follow-up. |
| – Normal physical examination, serum quantitative nontreponemal serologic titer ≤maternal titer, mother's treatment adequate before pregnancy | No treatment | No evaluation required.<br>Some experts would treat with benzathine penicillin G 50,000 U/kg as a single IM injection, particularly if follow-up is uncertain. |
| **Syphilis, congenital (>1 mo of age)**[94] | Aqueous crystalline penicillin G 200,000–300,000 U/kg/day IV div q4–6h for 10 days (AII) | Evaluation to determine type and duration of therapy: CSF analysis (VDRL, cell count, protein), CBC and platelet count. Other tests as clinically indicated, including long-bone radiographs, chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and hearing evaluation. If no clinical manifestations of disease, CSF examination is normal, and CSF VDRL test result is nonreactive, some specialists would treat with up to 3 weekly doses of benzathine penicillin G 50,000 U/kg IM. |

| | | |
|---|---|---|
| | | Some experts would provide a single dose of benzathine penicillin G 50,000 U/kg IM after 10 days of parenteral treatment, but value of this additional therapy is not well documented. |
| **Tetanus neonatorum**[95] | Metronidazole IV/PO (alternative: penicillin G IV) for 10–14 days (AIII)<br>Human TIG 3,000–6,000 U IM for 1 dose (AIII) | Wound cleaning and debridement vital; IVIG (200–400 mg/kg) is an alternative if TIG not available; equine tetanus antitoxin not available in the United States but is alternative to TIG. |
| **Toxoplasmosis, congenital**[96,97] | Sulfadiazine 100 mg/kg/day PO div q12h AND pyrimethamine 2 mg/kg PO daily for 2 days (loading dose), then 1 mg/kg PO q24h for 2–6 mo, then 3 times weekly (M-W-F) up to 1 y (AII)<br>Folinic acid (leucovorin) 10 mg 3 times weekly (AII) | Corticosteroids (1 mg/kg/day div q12h) if active chorioretinitis or CSF protein >1 g/dL (AIII).<br>Start sulfa after neonatal jaundice has resolved.<br>Therapy is only effective against active trophozoites, not cysts. |
| **Urinary tract infection**[98] | Initial empiric therapy with ampicillin AND gentamicin; OR ampicillin AND cefotaxime pending culture and susceptibility test results for 7–10 days | Investigate for kidney disease and abnormalities of urinary tract: VCUG indicated if renal ultrasound abnormal or after first UTI.<br>Oral therapy acceptable once neonate asymptomatic and culture sterile.<br>No prophylaxis for grades 1–3 reflux.[99]<br>In neonates with reflux, prophylaxis reduces recurrences but does not affect renal scarring.[99] |
| – Coliform bacteria (eg, *E coli, Klebsiella, Enterobacter, Serratia*) | Cefotaxime IV, IM OR, in absence of renal or perinephric abscess, gentamicin IV, IM for 7–10 days (AII) | Ampicillin used for susceptible organisms |
| – *Enterococcus* | Ampicillin IV, IM for 7 days for cystitis, may need 10–14 days for pyelonephritis, add gentamicin until cultures are sterile (AIII); for ampicillin resistance, use vancomycin, add gentamicin until cultures are sterile. | Aminoglycoside needed with ampicillin or vancomycin for synergistic bactericidal activity (assuming organisms susceptible to an aminoglycoside) |
| – *P aeruginosa* | Ceftazidime IV, IM OR, in absence of renal or perinephric abscess, tobramycin IV, IM for 7–10 days (AIII) | Meropenem or cefepime are alternatives. |

## A. RECOMMENDED THERAPY FOR SELECTED NEWBORN CONDITIONS (continued)

| Condition | Therapy (evidence grade)<br>*See Tables 5B–D for neonatal dosages.* | Comments |
|---|---|---|
| – *Candida* spp[31–33] | AmB-D IV OR fluconazole (if susceptible) (AII) | Neonatal *Candida* disease is often systemic with isolated *Candid;* therefore, isolated UTI less likely to occur and disease should be considered systemic. AmB-D has been shown in one retrospective study to be superior to AmB lipid formulations, but the lipid formulations are less toxic. However, the AmB lipid formulations theoretically have less penetration into the renal system compared with AmB-D.<br>Evaluate for other sites in high-risk neonates: CSF analysis; cardiac echo; abdominal ultrasound to include kidneys, bladder; eye examination.<br>Other triazoles are alternatives.<br>Echinocandins are not renally eliminated and should not be used to treat isolated neonatal UTI. |

## B. ANTIMICROBIAL DOSAGES FOR NEONATES—Lead author Jason Sauberan, assisted by the editors and John van den Anker

| | | Dosages (mg/kg/day) and Intervals of Administration | | | | |
|---|---|---|---|---|---|---|
| | | Chronologic Age ≤28 days | | | | |
| | | Body Weight ≤2,000 g | | Body Weight >2,000 g | | Chronologic Age |
| Antibiotic | Route | 0–7 days old | 8–28 days old | 0–7 days old | 8–28 days old | 29–60 days |
| **NOTE:** This table contains empiric dosage recommendations for each agent listed. Please see Table 5A (Recommended Therapy for Selected Newborn Conditions) for more precise details of optimal dosages for specific pathogens in specific tissue sites and for information on anti-influenza and antiretroviral drug dosages. | | | | | | |
| Acyclovir | IV[a] | 40 div q12h | 60 div q8h | 60 div q8h | 60 div q8h | 60 div q8h |
| | PO[b] | – | 900/$m^2$/day div q8h | – | 900/$m^2$/day div q8h | 900/$m^2$/day div q8h |
| Amoxicillin/clavulanate | PO | – | – | 30 div q12h | 30 div q12h | 30 div q12h |
| Amphotericin B | | | | | | |
| – deoxycholate | IV | 1 q24h | 1 q24h | 1 q24h | 1 q24h | 1 q24h |
| – lipid complex | IV | 5 q24h | 5 q24h | 5 q24h | 5 q24h | 5 q24h |
| – liposomal | IV | 5 q24h | 5 q24h | 5 q24h | 5 q24h | 5 q24h |
| Ampicillin[c] | IV, IM | 100 div q12h | 150 div q12h | 150 div q8h | 150 div q8h | 200 div q6h |
| Anidulafungin[d] | IV | 1.5 q24h[d] | 1.5 q24h[d] | 1.5 q24h[d] | 1.5 q24h[d] | 1.5 q24h[d] |
| Azithromycin[e] | PO | 10 q24h | 10 q24h | 10 q24h | 10 q24h | 10 q24h |
| | IV | 10 q24h | 10 q24h | 10 q24h | 10 q24h | 10 q24h |
| Aztreonam | IV, IM | 60 div q12h | 90 div q8h[f] | 60 div q12h | 90 div q8h | 120 div q6h |
| Caspofungin[g] | IV | 25/$m^2$ q24h | 25/$m^2$ q24h | 25/$m^2$ q24h | 25/$m^2$ q24h | 25/$m^2$ q24h |

**B. ANTIMICROBIAL DOSAGES FOR NEONATES** (continued)—Lead author Jason Sauberan, assisted by the editors and John van den Anker

| | | Dosages (mg/kg/day) and Intervals of Administration | | | | |
|---|---|---|---|---|---|---|
| | | Chronologic Age ≤28 days | | | | |
| | | Body Weight ≤2,000 g | | Body Weight >2,000 g | | Chronologic Age |
| Antibiotic | Route | 0–7 days old | 8–28 days old | 0–7 days old | 8–28 days old | 29–60 days |
| Cefazolin | IV, IM | 50 div q12h | 50 div q12h | 50 div q12h | 75 div q8h | 75 div q8h |
| Cefepime[h] | IV, IM | 100 div q12h | 150 div q8h[f] | 150 div q8h | 150 div q8h | 150 div q8h |
| Cefotaxime | IV, IM | 100 div q12h | 150 div q8h[f] | 100 div q12h | 150 div q8h | 200 div q6h |
| Cefoxitin | IV, IM | 70 div q12h | 100 div q8h[f] | 100 div q8h | 100 div q8h | 120 div q6h |
| Ceftazidime | IV, IM | 100 div q12h | 150 div q8h[f] | 100 div q12h | 150 div q8h | 150 div q8h |
| Ceftriaxone[i] | IV, IM | – | – | 50 q24h | 50 q24h | 50 q24h |
| Cefuroxime | IV, IM | 100 div q12h | 150 div q8h[f] | 100 div q12h | 150 div q8h | 150 div q8h |
| Chloramphenicol[j] | IV, IM | 25 q24h | 50 div q12h[f] | 25 q24h | 50 div q12h | 50–100 div q6h |
| Clindamycin | IV, IM, PO | 15 div q8h | 15 div q8h | 21 div q8h | 30 div q8h | 30 div q8h |
| Daptomycin (new concerns for neurologic toxicity in the newborn; use cautiously) | IV | 12 div q12h | 12 div q12h | 12 div q12h | 12 div q12h | 12 div q12h |
| Erythromycin | PO | 20 div q12h | 30 div q8h | 20 div q12h | 30 div q8h | 40 div q6h |
| Fluconazole | | | | | | |
| – treatment[k] | IV, PO | 12 q24h[k] | 12 q24h[k] | 12 q24h[k] | 12 q24h[k] | 12 q24h[k] |
| – prophylaxis | IV, PO | 6 mg/kg/dose twice weekly | 6 mg/kg/dose twice weekly | 6 mg/kg/dose twice weekly | 6 mg/kg/dose twice weekly | 6 mg/kg/dose twice weekly |

| | | | | | | |
|---|---|---|---|---|---|---|
| Flucytosine[l] | PO | 75 div q8h | 75 div q6h[f] | 75 div q6h | 75 div q6h | 75 div q6h |
| Ganciclovir | IV | Insufficient data | Insufficient data | 12 div q12h | 12 div q12h | 12 div q12h |
| Linezolid | IV, PO | 20 div q12h | 30 div q8h | 30 div q8h | 30 div q8h | 30 div q8h |
| Meropenem | | | | | | |
| – sepsis[m] | IV | 40 div q12h | 60 div q8h[m] | 60 div q8h | 90 div q8h[m] | 90 div q8h |
| – meningitis | IV | 120 div q8h | 120 div q8h | 120 div q8h | 120 div q8h | 120 div q8h |
| Metronidazole[n] | IV, PO | 15 div q12h | 15 div q12h | 22.5 div q8h | 30 div q8h | 30 div q8h |
| Micafungin | IV | 10 q24h | 10 q24h | 10 q24h | 10 q24h | 10 q24h |
| Nafcillin,[o] oxacillin[o] | IV, IM | 50 div q12h | 75 div q8h[f] | 75 div q8h | 100 div q6h | 150 div q6h |
| Penicillin G benzathine | IM | 50,000 U | 50,000 U | 50,000 U | 50,000 U | 50,000 U |
| Penicillin G crystalline (congenital syphilis) | IV | 100,000 U div q12h | 150,000 U[f] div q8h | 100,000 U div q12h | 150,000 U div q8h | 200,000 U div q6h |
| Penicillin G crystalline (GBS meningitis) | IV | 200,000 U div q12h | 300,000 U[f] div q8h | 300,000 U div q8h | 400,000 U div q6h | 400,000 U div q6h |
| Penicillin G procaine | IM | 50,000 U q24h | 50,000 U q24h | 50,000 U q24h | 50,000 U q24h | 50,000 U q24h |
| Piperacillin/tazobactam | IV | 300 div q8h | 320 div q6h | 320 div q6h | 320 div q6h | 320 div q6h |
| Rifampin | IV, PO | 10 q24h | 10 q24h | 10 q24h | 10 q24h | 10 q24h |
| Ticarcillin/clavulanate | IV | 150 div q12h | 225 div q8h[f] | 150 div q12h | 225 div q8h | 300 div q6h |
| Valganciclovir | PO | Insufficient data | Insufficient data | 32 div q12h | 32 div q12h | 32 div q12h |
| Voriconazole[p] | IV, PO | 18 div q12h | 18 div q12h | 18 div q12h | 18 div q12h | 18 div q12h |

## B. ANTIMICROBIAL DOSAGES FOR NEONATES (continued)—Lead author Jason Sauberan, assisted by the editors and John van den Anker

| | | Dosages (mg/kg/day) and Intervals of Administration | | | | |
|---|---|---|---|---|---|---|
| | | Chronologic Age ≤28 days | | | | |
| | | Body Weight ≤2,000 g | | Body Weight >2,000 g | | Chronologic Age 29–60 days |
| Antibiotic | Route | 0–7 days old | 8–28 days old | 0–7 days old | 8–28 days old | |
| Zidovudine | IV | 3 div q12h[q] | 3 div q12h[q] | 6 div q12h | 6 div q12h | See Table 5A, HIV. |
| | PO | 4 div q12h[q] | 4 div q12h[q] | 8 div q12h | 8 div q12h | See Table 5A, HIV. |

[a] Only parenteral acyclovir should be used for the treatment of acute neonatal HSV disease.

[b] Oral suppression therapy for 6 months after initial neonatal HSV treatment. Dosing units are mg/m$^2$/day.

[c] 300 mg/kg/day for GBS meningitis div q8h for all neonates ≤7 days of age and q6h >7 days of age.

[d] Loading dose 3 mg/kg followed 24 hours later by maintenance dose listed.

[e] Azithromycin oral dose for pertussis should be 10 mg/kg once daily for the entire 5-day treatment course, while for other upper respiratory tract infections, 10 mg/kg is given on the first day, followed by 5 mg/kg once daily for 4 days. For CNS disease, 10 mg/kg once daily for entire course.

[f] Use 0–7 days of age frequency until 14 days of age if birth weight <1,000 g.

[g] Dosing units are mg/m$^2$. Higher dosage of 50 mg/m$^2$ may be needed for *Aspergillus.*

[h] Doses listed are for meningitis or *Pseudomonas* infections. Can give 60 mg/kg/day div q12h for treatment of non-CNS infections caused by enteric bacilli (eg, *E coli, Klebsiella, Enterobacter, Serratia*), as they are more susceptible to cefepime than *Pseudomonas.*

[i] Usually avoided in neonates. Can be considered for transitioning to outpatient treatment of GBS bacteremia in well-appearing neonates at low risk for hyperbilirubinemia.

[j] Desired serum concentration 15–25 mg/mL.

[k] Loading dose 25 mg/kg followed 24 hours later by maintenance dose listed.

[l] Desired serum concentrations peak 50–100 mg/L, trough 25–50 mg/L.

[m] Adjust dosage after 14 days of age instead of after 7 days of age.

[n] Loading dose 15 mg/kg.

[o] Increase to 50 mg/kg/dose for meningitis.

[p] Initial loading dose of 18 mg/kg div q12h on day 1. Desired serum concentrations, trough 2–6 µg/mL.

[q] Starting dose if gestational age <35+0 wk and postnatal ≤14 days. See Table 5A, HIV, for zidovudine dosage after 2 weeks of age and for NVP and 3TC recommendations.

## C. AMINOGLYCOSIDES

**Empiric Dosage (mg/kg/dose) by Gestational and Postnatal Age**

| | | <30 wk | | 30–34 wk | | ≥35 wk | |
|---|---|---|---|---|---|---|---|
| **Medication** | **Route** | **0–14 days** | **>14 days** | **0–10 days** | **>10 days[a]** | **0–7 days** | **>7 days[a]** |
| Amikacin[b] | IV, IM | 15 q48h | 15 q24h | 15 q24h | 15 q24h | 15 q24h | 17.5 q24h |
| Gentamicin[c] | IV, IM | 5 q48h | 5 q36h | 4.5 q36h | 5 q36h | 4 q24h | 5 q24h |
| Tobramycin[c] | IV, IM | 5 q48h | 5 q36h | 4.5 q36h | 5 q36h | 4 q24h | 5 q24h |

[a] At >60 days of age, can consider amikacin 15–20 mg/kg q24h and gentamicin/tobramycin 4.5–7.5 mg/kg q24h (see Chapter 11).

[b] Desired serum concentrations: 20–35 mg/L (peak), <7 mg/L (trough).

[c] Desired serum concentrations: 6–12 mg/L (peak), <2 mg/L (trough).

## D. VANCOMYCIN[a]

**Empiric Dosage[b,c] (mg/kg/dose) by Gestational Age and Serum Creatinine**

| ≤28 wk | | | >28 wk | | |
|---|---|---|---|---|---|
| **Serum Creatinine** | **Dose** | **Frequency** | **Serum Creatinine** | **Dose** | **Frequency** |
| <0.5 | 15 | q12h | <0.7 | 15 | q12h |
| 0.5–0.7 | 20 | q24h | 0.7–0.9 | 20 | q24h |
| 0.8–1 | 15 | q24h | 1–1.2 | 15 | q24h |
| 1.1–1.4 | 10 | q24h | 1.3–1.6 | 10 | q24h |
| >1.4 | 15 | q48h | >1.6 | 15 | q48h |

[a] Serum creatinine concentrations normally fluctuate and are partly influenced by transplacental maternal creatinine in the first week of age. Cautious use of creatinine-based dosing strategy with frequent reassessment of renal function and vancomycin serum concentrations are recommended in neonates ≤7 days old.

[b] Up through 60 days of age. If >60 days of age, 45–60 mg/kg/day div q8h (see Chapter 11).

[c] Desired serum concentrations vary by pathogen, site of infection, degree of illness; for MRSA and MSSA, aim for a target based on the ratio of the area under the curve–minimum inhibitory concentration of ~400 mg/L × hr, which will require peak and trough measurement. For coagulase-negative staphylococci and *Enterococcus,* troughs of 5–10 mg/L are likely to be effective.

## E. Use of Antimicrobials During Pregnancy or Breastfeeding

The use of antimicrobials during pregnancy should be balanced by the risk of fetal toxicity, including anatomic anomalies. A number of factors determine the degree of transfer of antibiotics across the placenta: lipid solubility, degree of ionization, molecular weight, protein binding, placental maturation, and placental and fetal blood flow. The FDA provides 5 categories to indicate the level of risk to the fetus: (1) Category A: fetal harm seems remote, as controlled studies have not demonstrated a risk to the fetus; (2) Category B: animal reproduction studies have not shown a fetal risk, but no controlled studies in pregnant women have been done, or animal studies have shown an adverse effect that has not been confirmed in human studies (penicillin, amoxicillin, ampicillin, cephalexin/cefazolin, azithromycin, clindamycin, vancomycin, zanamivir); (3) Category C: studies in animals have shown an adverse effect on the fetus, but there are no studies in women; the potential benefit of the drug may justify the possible risk to the fetus (chloramphenicol, ciprofloxacin, gentamicin, levofloxacin, oseltamivir, rifampin); (4) Category D: evidence exists of human fetal risk, but the benefits may outweigh such risk (doxycycline); (5) Category X: the drug is contraindicated because animal or human studies have shown fetal abnormalities or fetal risk (ribavirin). Prescription drugs approved after June 30, 2015, are required to conform to a new pregnancy risk labeling format. See www.federalregister.gov/a/2014-28241.

Fetal serum antibiotic concentrations (or cord blood concentrations) following maternal administration have not been systematically studied.[100] The following commonly used drugs appear to achieve fetal concentrations that are equal to or only slightly less than those in the mother: penicillin G, amoxicillin, ampicillin, sulfonamides, trimethoprim, and tetracyclines, as well as oseltamivir.[101] The aminoglycoside concentrations in fetal serum are 20% to 50% of those in maternal serum. Cephalosporins, carbapenems, nafcillin, oxacillin, clindamycin, and vancomycin[102] penetrate poorly (10%–30%), and fetal concentrations of erythromycin and azithromycin are less than 10% of those in the mother.

The most current, updated information on the safety of antimicrobials and other agents in human milk can be found at the National Library of Medicine LactMed Web site (http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm, accessed August 27, 2015).[103]

In general, neonatal exposure to antimicrobials in human milk is minimal or insignificant. Aminoglycosides, beta-lactams, ciprofloxacin, clindamycin, macrolides, fluconazole, and agents for tuberculosis are considered safe for the mother to take during breastfeeding.[104] The most common reported neonatal side effect of maternal antimicrobial use during breastfeeding is increased stool output. Clinicians should recommend mothers alert their pediatric health care professional if stool output changes occur. Maternal treatment with sulfa-containing antibiotics should be approached with caution in the breastfed infant who is jaundiced or ill.

## 6. Antimicrobial Therapy According to Clinical Syndromes

### NOTES

- This chapter should be considered a rough guidance for a typical patient. Dosage recommendations are for patients with relatively normal hydration, renal function, and hepatic function. Higher dosages may be necessary if the antibiotic does not penetrate well into the infected tissue (eg, meningitis) or if the child is immunocompromised.
- Duration of treatment should be individualized. Those recommended are based on the literature, common practice, and general experience. Critical evaluations of duration of therapy have been carried out in very few infectious diseases. In general, a longer duration of therapy should be used (1) for tissues in which antibiotic concentrations may be relatively low (eg, undrained abscess, central nervous system [CNS] infection); (2) for tissues in which repair following infection-mediated damage is slow (eg, bone); (3) when the organisms are less susceptible; (4) when a relapse of infection is unacceptable (eg, CNS infections); or (5) when the host is immunocompromised in some way. An assessment after therapy will ensure that your selection of antibiotic, dose, and duration of therapy were appropriate.
- Diseases in this chapter are arranged by body systems. Consult the index for the alphabetized listing of diseases and chapters 7 through 10 for the alphabetized listing of pathogens and for uncommon organisms not included in this chapter.
- A more detailed description of treatment of methicillin-resistant *Staphylococcus aureus* infections is provided in Chapter 4.
- Therapy of *Pseudomonas aeruginosa* systemic infections is evolving from intravenous (IV) ceftazidime plus tobramycin to single drug IV therapy with cefepime due to the relative stability of cefepime to beta-lactamases, compared with ceftazidime. Oral therapy with ciprofloxacin is often replacing IV therapy in otherwise normal children who are compliant and able to take oral therapy, particularly for "step-down" therapy of invasive infections.
- **Abbreviations:** AAP, American Academy of Pediatrics; ADH, antidiuretic hormone; AFB, acid-fast bacilli; ALT, alanine transaminase; AmB, amphotericin B; amox/clav, amoxicillin/clavulanate; AOM, acute otitis media; ARF, acute rheumatic fever; AST, aspartate transaminase; AUC:MIC, area under the curve–minimum inhibitory concentration; bid, twice daily; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus;* CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; CNS, central nervous system; CRP, C-reactive protein; CSD, cat-scratch disease; CSF, cerebrospinal fluid; CT, computed tomography; DAT, diphtheria antitoxin; div, divided; DOT, directly observed therapy; EBV, Epstein-Barr virus; ELF, epithelial lining fluid (in lung airways); ESBL, extended spectrum beta-lactamase; ESR, erythrocyte sedimentation rate; ETEC, enterotoxin-producing *Escherichia coli;* FDA, US Food and Drug Administration; GI, gastrointestinal; HACEK, *Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis,*

*Eikenella corrodens, Kingella* spp; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HUS, hemolytic uremic syndrome; I&D, incision and drainage; IDSA, Infectious Diseases Society of America; IM, intramuscular; INH, isoniazid; IV, intravenous; IVIG, intravenous immune globulin; KPC, *Klebsiella pneumoniae* carbapenemase; LFT, liver function test; LP, lumbar puncture; MDR, multidrug resistant; MRSA, methicillin-resistant *S aureus;* MRSE, methicillin-resistant *Staphylococcus epidermidis;* MSSA, methicillin-susceptible *S aureus;* MSSE, methicillin-sensitive *S epidermidis;* NIH, National Institutes of Health; ophth, ophthalmic; PCR, polymerase chain reaction; PCV13, Prevnar 13-valent pneumococcal conjugate vaccine; pen-R, penicillin-resistant; pen-S, penicillin-susceptible; PIDS, Pediatric Infectious Diseases Society; pip/tazo, piperacillin/tazobactam; PO, oral; PPD, purified protein derivative; PZA, pyrazinamide; qd, once daily; qid, 4 times daily; qod, every other day; RIVUR, Randomized Intervention for Children with Vesicoureteral Reflux; RSV, respiratory syncytial virus; SPAG-2, small particle aerosol generator-2; spp, species; STEC, Shiga toxin–producing *E coli;* STI, sexually transmitted infection; TB, tuberculosis; Td, tetanus-diphtheria; Tdap, tetanus-diphtheria-acellular pertussis; ticar/clav, ticarcillin/clavulanate; tid, 3 times daily; TIG, tetanus immune globulin; TMP/SMX, trimethoprim/sulfamethoxazole; ULN, upper limit of normal; UTI, urinary tract infection; VDRL, Venereal Disease Research Laboratories; WBC, white blood cell.

## A. SKIN AND SOFT TISSUE INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **NOTE:** CA-MRSA (see Chapter 4) is increasingly prevalent in most areas of the world. Recommendations are given for 2 scenarios: standard and CA-MRSA. Antibiotic recommendations for CA-MRSA should be used for empiric therapy in regions with greater than 5% to 10% of serious staphylococcal infections caused by MRSA, in situations where CA-MRSA is suspected, and for documented CA-MRSA infections, while standard recommendations refer to treatment of MSSA. During the past few years, clindamycin resistance in MRSA has increased to 40% in some areas but remained stable at 5% in others, although this increase may be an artifact of changes in reporting, with many laboratories now reporting all clindamycin-susceptible but D-test–positive strains as resistant. Please check your local susceptibility data for *S aureus* before using clindamycin for empiric therapy. For MSSA, oxacillin/nafcillin are considered equivalent agents. | | |
| **Adenitis, acute bacterial**[1–7] (*S aureus*, including CA-MRSA, and group A streptococcus; consider *Bartonella* [CSD] for subacute adenitis)[8] | Empiric therapy:<br>Standard: oxacillin/nafcillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (AI), OR cephalexin 50–75 mg/kg/day PO div tid<br>CA-MRSA: clindamycin 30 mg/kg/day IV or PO div q8h OR vancomycin 40 mg/kg/day IV q8h (BII)<br>CSD: azithromycin 12 mg/kg once daily (max 500 mg) for 5 days (BIII) | May need surgical drainage for staph/strep infection; not usually needed for CSD.<br>Following drainage of mild to moderate suppurative adenitis caused by staph or strep, additional antibiotics may not be required.<br>For oral therapy for MSSA: cephalexin or amox/clav; for CA-MRSA: clindamycin, TMP/SMX, or linezolid.<br>For oral therapy of group A strep: amoxicillin or penicillin V.<br>Total IV plus PO therapy for 7–10 days.<br>For CSD: this is the same high dose of azithromycin that is recommended routinely for strep pharyngitis. |
| **Adenitis, nontuberculous (atypical) mycobacterial**[9–12] | Excision usually curative (BII); azithromycin PO OR clarithromycin PO for 6–12 wk (with or without rifampin) if susceptible (BII) | Antibiotic susceptibility patterns are quite variable; cultures should guide therapy; medical therapy 60%–70% effective. Newer data suggest toxicity of antimicrobials may not be worth the small clinical benefit of medical therapy over surgery. |

## A. SKIN AND SOFT TISSUE INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Adenitis, tuberculous**[13,14] (*M tuberculosis* and *M bovis*) | INH 10–15 mg/kg/day (max 300 mg) PO, IV qd, for 6 mo AND rifampin 10–20 mg/kg/day (max 600 mg) PO, IV qd, for 6 mo AND PZA 20–40 mg/kg/day PO qd for first 2 mo therapy (BI); if suspected multidrug resistance, add ethambutol 20 mg/kg/day PO qd. | Surgical excision usually not indicated because organisms are treatable.<br>Adenitis caused by *Mycobacterium bovis* (unpasteurized dairy product ingestion) is uniformly resistant to PZA. Treat 9–12 mo with INH and rifampin, if susceptible (BII). |
| **Anthrax, cutaneous**[15] | Empiric therapy: ciprofloxacin 20–30 mg/kg/day PO div bid OR doxycycline 4 mg/kg/day (max 200 mg) PO div bid (regardless of age) (AIII) | If susceptible, amoxicillin or clindamycin (BIII). Ciprofloxacin and levofloxacin are FDA approved for inhalational anthrax (BIII). |
| **Bites, animal and human**[1,16–19] *Pasteurella multocida* (animal), *Eikenella corrodens* (human), *Staphylococcus* spp, and *Streptococcus* spp | Amox/clav 45 mg/kg/day PO div tid (amox/clav 7:1; see Chapter 1, Aminopenicillins) for 5–10 days (AII); for hospitalized children, use ticar/clav 200 mg ticarcillin/kg/day div q6h OR ampicillin and clindamycin (BII). For penicillin allergy, ciprofloxacin (for *Pasteurella*) plus clindamycin (BIII). | Consider rabies prophylaxis[20] for bites from at-risk animals (observe animal for 10 days, if possible) (AI); consider tetanus prophylaxis.<br>Human bites have a very high rate of infection (do not close open wounds).<br>*S aureus* (MSSA) coverage is only fair with amox/clav, ticar/clav; no MRSA coverage. |
| **Bullous impetigo**[1–3,5–7] (usually *S aureus,* including CA-MRSA) | Standard: cephalexin 50–75 mg/kg/day PO div tid OR amox/clav 45 mg/kg/day PO div tid (CII)<br>CA-MRSA: clindamycin 30 mg/kg/day PO div tid OR TMP/SMX 8 mg/kg/day of TMP PO div bid; for 5–7 days (CI) | For topical therapy if mild infection: mupirocin or retapamulin ointment |
| **Cellulitis of unknown etiology** (usually *S aureus,* including CA-MRSA, or group A streptococcus)[1–7,21] | Empiric IV therapy:<br>Standard: oxacillin/nafcillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (BII)<br>CA-MRSA: clindamycin 30 mg/kg/day IV div q8h OR vancomycin 40 mg/kg/day IV q8h (BII) | For periorbital or buccal cellulitis, also consider *Streptococcus pneumoniae* or *Haemophilus influenzae* type b in unimmunized infants.<br>Total IV plus PO therapy for 7–10 days. |

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| | For oral therapy for MSSA: cephalexin (AII) OR amox/clav 45 mg/kg/day PO div tid (BII); for CA-MRSA: clindamycin (BII), TMP/SMX (AII), or linezolid (BII) | |
| **Cellulitis, buccal** (for unimmunized infants and preschool-aged children, *H influenzae* type b)[22] | Cefotaxime 100–150 mg/kg/day IV div q8h OR ceftriaxone 50 mg/kg/day (AI) IV, IM q24h; for 2–7 days parenteral therapy before switch to oral (BII) | Rule out meningitis (larger dosages may be needed).<br>For penicillin allergy, levofloxacin IV/PO covers pathogens, but no clinical data available; safer than chloramphenicol.<br>Oral therapy: amoxicillin if beta-lactamase negative; amox/clav or oral 2nd- or 3rd-generation cephalosporin if beta-lactamase positive. |
| **Cellulitis, erysipelas** (streptococcal)[1,2,7] | Penicillin G 100,000–200,000 U/kg/day IV div q4–6h (BII) initially then penicillin V 100 mg/kg/day PO div qid (BIII) or tid OR amoxicillin 50 mg/kg/day PO div tid (BIII) for 10 days | These dosages may be unnecessarily large, but there is little clinical experience with smaller dosages. |
| **Gas gangrene** (See Necrotizing fasciitis.) | | |
| **Impetigo** (*S aureus,* including CA-MRSA; occasionally group A streptococcus)[1,2,6,7,23,24] | Mupirocin OR retapamulin topically (BII) to lesions tid; OR for more extensive lesions, oral therapy:<br>Standard: cephalexin 50–75 mg/kg/day PO div tid OR amox/clav 45 mg/kg/day PO div tid (AII)<br>CA-MRSA: clindamycin 30 mg/kg/day (CII) PO div tid OR TMP/SMX 8 mg/kg/day TMP PO div bid (AI); for 5–7 days | Cleanse infected area with soap and water. |
| **Ludwig angina**[25] | Penicillin G 200,000–250,000 U/kg/day IV div q6h AND clindamycin 40 mg/kg/day IV div q8h (CIII) | Alternatives: meropenem, imipenem, ticar/clav, pip/tazo if gram-negative aerobic bacilli also suspected (CIII); high risk of respiratory tract obstruction from inflammatory edema |
| **Lymphadenitis** (See Adenitis, acute bacterial.) | | |

## A. SKIN AND SOFT TISSUE INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Lymphangitis, blistering dactylitis** (usually group A streptococcus)[1,2,7] | Penicillin G 200,000 U/kg/day IV div q6h (BII) initially, then penicillin V 100 mg/kg/day PO div qid OR amoxicillin 50 mg/kg/day PO div tid for 10 days | For mild disease, penicillin V 50 mg/kg/day PO div qid for 10 days<br>Some recent reports of *S aureus* as a cause |
| **Myositis, suppurative**[26] (*S aureus,* including CA-MRSA; synonyms: tropical myositis, pyomyositis) | Standard: oxacillin/nafcillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (CII)<br>CA-MRSA: clindamycin 40 mg/kg/day IV div q8h OR vancomycin 40 mg/kg/day IV q8h (CIII) | Aggressive, emergent debridement; use clindamycin to help decrease toxin production (BIII); consider IVIG to bind bacterial toxins for life-threatening disease (CIII); abscesses may develop with CA-MRSA while on therapy. |
| **Necrotizing fasciitis** (Pathogens vary depending on the age of the child and location of infection. Single pathogen: group A streptococcus; *Clostridia* spp, *S aureus* [including CA-MRSA], *Pseudomonas aeruginosa, Vibrio* spp, *Aeromonas.* Multiple pathogen, mixed aerobic/anaerobic synergistic fasciitis: any organism[s] above, plus gram-negative bacilli, plus *Bacteroides* spp, and other anaerobes.)[1,27–30] | Empiric therapy: ceftazidime 150 mg/kg/day IV div q8h, or cefepime 150 mg/kg/day IV div q8h or cefotaxime 200 mg/kg/day IV div q6h AND clindamycin 40 mg/kg/day IV div q8h (BIII); OR meropenem 60 mg/kg/day IV div q8h; OR pip/tazo 400 mg/kg/day pip component IV div q6h (AIII).<br>ADD vancomycin for suspect CA-MRSA, pending culture results (AIII).<br>Group A streptococcal: penicillin G 200,000–250,000 U/kg/day div q6h AND clindamycin 40 mg/kg/day div q8h (AIII).<br>Mixed aerobic/anaerobic/gram-negative: meropenem or pip/tazo AND clindamycin (AIII). | Aggressive emergent wound debridement (AII).<br>Add clindamycin to inhibit synthesis of toxins during the first few days of therapy (AIII).<br>If CA-MRSA identified and susceptible to clindamycin, additional vancomycin is not required.<br>Consider IVIG to bind bacterial toxins for life-threatening disease (BIII).<br>Value of hyperbaric oxygen is not established (CIII).<br>Focus definitive antimicrobial therapy based on culture results. |
| **Pyoderma, cutaneous abscesses** (*S aureus,* including CA-MRSA; group A streptococcus)[2,5–7,21,31–33] | Standard: cephalexin 50–75 mg/kg/day PO div tid OR amox/clav 45 mg/kg/day PO div tid (BII)<br>CA-MRSA: clindamycin 30 mg/kg/day PO div tid (BII) OR TMP/SMX 8 mg/kg/day of TMP PO div bid (AI) | I&D when indicated; IV for serious infections.<br>For prevention of recurrent CA-MRSA infection, use bleach baths twice weekly (½ cup of bleach per full bathtub) (BII), OR bathe with chlorhexidine soap daily or qod (BIII). Decolonization with mupirocin may also be helpful. |

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| **Rat-bite fever**<br>(*Streptobacillus moniliformis, Spirillum minus*)[34] | Penicillin G 100,000–200,000 U/kg/day IV div q6h (BII) for 7–10 days; for endocarditis, ADD gentamicin for 4–6 wk (CIII).<br>For mild disease, oral therapy with amox/clav (CIII). | Organisms are normal oral flora for rodents.<br>High rate of associated endocarditis.<br>Alternatives: doxycycline; 2nd- and 3rd-generation cephalosporins (CIII). |
| **Staphylococcal scalded skin syndrome**[6,35] | Standard: oxacillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (CII)<br>CA-MRSA: clindamycin 30 mg/kg/day IV div q8h (CIII) or vancomycin 40 mg/kg/day IV q8h (CIII) | Burow or Zephiran compresses for oozing skin and intertriginous areas.<br>Corticosteroids are contraindicated. |

## B. SKELETAL INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **NOTE:** CA-MRSA (see Chapter 4) is increasingly prevalent in most areas of the world. Recommendations are given for CA-MRSA and MSSA. Antibiotic recommendations for empiric therapy should include CA-MRSA when it is suspected or documented, while treatment for MSSA with beta-lactam antibiotics (eg, cephalexin) is preferred over clindamycin. During the past few years, clindamycin resistance in MRSA has increased to 40% in some areas but remained stable at 5% in others, although this increase may be an artifact of changes in reporting, with many laboratories now reporting all clindamycin-susceptible but D-test–positive strains as resistant. Please check your local susceptibility data for *S aureus* before using clindamycin for empiric therapy. For MSSA, oxacillin/nafcillin are considered equivalent agents. The first pediatric-specific PIDS/IDSA guidelines for bacterial osteomyelitis and bacterial arthritis are currently being written. | | |
| **Arthritis, bacterial**[36–40] | Switch to appropriate high-dose oral therapy when clinically improved, CRP decreasing (see Chapter 13).[41] | |
| **– Newborns** | See Chapter 5. | |
| – Infants (*S aureus,* including CA-MRSA; group A streptococcus; *Kingella kingae;* in unimmunized or immunocompromised children: pneumococcus, *H influenzae* type b)<br>– Children (*S aureus,* including CA-MRSA; group A streptococcus; *K kingae*) | Empiric therapy: clindamycin (to cover CA-MRSA unless clindamycin resistance locally is >10%, then use vancomycin).<br>For serious infections, ADD cefazolin to provide better MSSA coverage and add *Kingella* coverage.<br>For CA-MRSA: clindamycin 30 mg/kg/day IV div q8h OR vancomycin 40 mg/kg/day IV q8h.<br>For MSSA: oxacillin/nafcillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h.<br>For *Kingella:* cefazolin 100 mg/kg/day IV div q8h OR ampicillin 150 mg/kg/day IV div q6h, OR ceftriaxone 50 mg/kg/day IV, IM q24h.<br>For pen-S pneumococci or group A streptococcus: penicillin G 200,000 U/kg/day IV div q6h.<br>For pen-R pneumococci or *Haemophilus:* ceftriaxone 50–75 mg/kg/day IV, IM q24h, OR cefotaxime (BII).<br>Total therapy (IV plus PO) for up to 21 days with normal ESR; low-risk, non-hip MSSA arthritis may respond to a 10-day course.[37,38] | Oral therapy options:<br>For CA-MRSA: clindamycin OR linezolid[40]<br>For MSSA: cephalexin OR cloxacillin caps for older children<br>For *Kingella,* most penicillins or cephalosporins (but not clindamycin) |

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| – Gonococcal arthritis or tenosynovitis[42,43] | Ceftriaxone 50 mg/kg IV, IM q24h (BII) for 7 days AND azithromycin 20 mg/kg PO as a single dose | Combination therapy with azithromycin to decrease risk of development of resistance.<br>Cefixime 8 mg/kg/day PO as a single daily dose may not be effective due to increasing resistance. Ceftriaxone IV, IM is preferred over cefixime PO. |
| – Other bacteria | See Chapter 7 for preferred antibiotics. | |
| **Osteomyelitis**[36,39,40,44–49] | Step down to appropriate high-dose oral therapy when clinically improved (See Chapter 13.)[40,47] | |
| – Newborns | See Chapter 5. | |
| – Infants and children, acute infection (usually *S aureus,* including CA-MRSA; group A streptococcus; *K kingae*) | Empiric therapy: clindamycin (for coverage of MSSA and MRSA in most locations).<br>For serious infections, ADD cefazolin to provide better MSSA coverage and add *Kingella* coverage (CIII).<br>For CA-MRSA: clindamycin 30 mg/kg/day IV div q8h or vancomycin 40 mg/kg/day IV q8h (BII).<br>For MSSA: oxacillin/nafcillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (AII).<br>For *Kingella:* cefazolin 100 mg/kg/day IV div q8h OR ampicillin 150 mg/kg/day IV div q6h, OR ceftriaxone 50 mg/kg/day IV, IM q24h (BIII).<br>Total therapy (IV plus PO) usually 4–6 wk for MSSA (with end-of-therapy normal ESR, radiograph to document healing) but may be as short as 3 wk for mild infection. May need longer than 4–6 wk for CA-MRSA (BII).<br>Follow closely for clinical response to empiric therapy. | In children with open fractures secondary to trauma, add ceftazidime for extended aerobic gram-negative bacilli activity.<br>*Kingella* is often resistant to clindamycin and vancomycin.<br>For MSSA (BI) and *Kingella* (BIII), step-down oral therapy with cephalexin 100 mg/kg/day PO div tid.<br>Oral step-down therapy alternatives for CA-MRSA include clindamycin and linezolid,[50] with insufficient data to recommend TMP/SMX. |
| – Acute, other organisms | See Chapter 7 for preferred antibiotics. | |

## B. SKELETAL INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – Chronic (staphylococcal) | For MSSA: cephalexin 100 mg/kg/day PO div tid OR dicloxacillin caps 75–100 mg/kg/day PO div qid for 3–6 mo or longer (CIII)<br>For CA-MRSA: clindamycin or linezolid (CIII) | Surgery to debride sequestrum is usually required for cure. For prosthetic joint infection caused by staphylococci, add rifampin (CIII).[48]<br>Watch for beta-lactam–associated neutropenia with high-dose, long-term therapy and linezolid-associated neutropenia/thrombocytopenia with long-term (>2 wk) therapy.[50] |
| **Osteomyelitis of the foot**[51] (osteochondritis after a puncture wound)<br>*P aeruginosa* (occasionally *S aureus,* including CA-MRSA) | Ceftazidime 150 mg/kg/day IV, IM div q8h AND tobramycin 6–7.5 mg/kg/day IM, IV div q8h (BIII); OR cefepime 150 mg/kg/day IV div q8h (BIII); OR meropenem 60 mg/kg/day IV div q8h (BIII); ADD vancomycin 40 mg/kg/day IV q8h for serious infection (for CA-MRSA), pending culture results. | Thorough surgical debridement required (2nd drainage procedure needed in at least 20% of children); oral convalescent therapy with ciprofloxacin (BIII)[52]<br>Treatment course 7–10 days after surgery |

## C. EYE INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Cellulitis, orbital**[53–55] (usually secondary to sinus infection; caused by respiratory tract flora and *S aureus,* including CA-MRSA) | Cefotaxime 150 mg/kg/day div q8h or ceftriaxone 50 mg/kg/day q24h; ADD clindamycin 30 mg/kg/day IV div q8h (for *S aureus,* including CA-MRSA) OR vancomycin 40 mg/kg/day IV q8h (AIII). If MSSA isolated, use oxacillin/nafcillin IV OR cefazolin IV. | Surgical drainage of larger collections of pus, if present by CT scan in orbit or subperiosteal tissue. Try medical therapy alone for small abscess (BIII).[56]<br>Treatment course for 10–14 days after surgical drainage, up to 21 days. CT scan to confirm cure (BIII). |
| **Cellulitis, periorbital**[57] (preseptal infection) | | |

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| – Associated with entry site lesion on skin (*S aureus,* including CA-MRSA, group A streptococcus) in the fully immunized child | Standard: oxacillin/nafcillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (BII)<br>CA-MRSA: clindamycin 30 mg/kg/day IV div q8h or vancomycin 40 mg/kg/day IV q8h (BIII) | Oral antistaphylococcal antibiotic (eg, clindamycin) for empiric therapy of less severe infection; treatment course for 7–10 days |
| – No associated entry site (in febrile, unimmunized infants): pneumococcal or *H influenzae* type b | Ceftriaxone 50 mg/kg/day q24h OR cefotaxime 100–150 mg/kg/day IV, IM div q8h OR cefuroxime 150 mg/kg/day IV div q8h (AII) | Treatment course for 7–10 days; rule out meningitis; alternative: other 2nd-, 3rd-, or 4th-generation cephalosporins or chloramphenicol. |
| – Periorbital, non-tender erythematous swelling (not true cellulitis, usually associated with sinusitis); sinus pathogens *rarely* may erode anteriorly, causing cellulitis. | Ceftriaxone 50 mg/kg/day q24h OR cefotaxime 100–150 mg/kg/day IV, IM div q8h OR cefuroxime 150 mg/kg/day IV div q8h (BIII).<br>ADD clindamycin 30 mg/kg/day IV div q8h for more severe infection with suspect *S aureus* including CA-MRSA or for chronic sinusitis (covers anaerobes) (AIII). | For oral convalescent antibiotic therapy, see Sinusitis, acute; total treatment course of 14–21 days or 7 days after resolution of symptoms. |
| **Conjunctivitis, acute** (*Haemophilus* and pneumococcus predominantly)[58–60] | Polymyxin/trimethoprim ophth solution OR polymyxin/bacitracin ophth ointment OR ciprofloxacin ophth solution (BII), for 7–10 days.<br>For neonatal infection, see Chapter 5.<br>Steroid-containing therapy only if HSV ruled out. | Other topical antibiotics (gentamicin, tobramycin ophth solution erythromycin, besifloxacin, moxifloxacin, norfloxacin, ofloxacin, levofloxacin) may offer advantages for particular pathogens (CII).<br>High rates of resistance to sulfacetamide. |
| **Conjunctivitis, herpetic**[61–63] | 1% trifluridine or 0.15% ganciclovir ophth gel (AII) AND acyclovir PO (80 mg/kg/day div qid; max daily dose: 3,200 mg/day) has been effective in limited studies (BIII). | Refer to ophthalmologist. Recurrences common; corneal scars may form. Topical steroids for keratitis concurrent with topical antiviral solution.<br>Long-term prophylaxis for suppression of recurrent infection with oral acyclovir 300 mg/m$^2$/dose PO tid (max 400 mg/dose) (little long-term safety data in children). Assess for neutropenia on long-term therapy; potential risks must balance potential benefits to vision (BIII). |

## C. EYE INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Dacryocystitis** | No antibiotic usually needed; oral therapy for more symptomatic infection, based on Gram stain and culture of pus; topical therapy as for conjunctivitis may be helpful. | Warm compresses; may require surgical probing of nasolacrimal duct |
| **Endophthalmitis**[64,65] | | |
| **NOTE:** Subconjunctival/sub-tenon antibiotics are likely to be required (vancomycin/ceftazidime or clindamycin/gentamicin); steroids commonly used; requires anterior chamber or vitreous tap for microbiological diagnosis. Listed systemic antibiotics to be used in addition to ocular injections. | | Refer to ophthalmologist; vitrectomy may be necessary for advanced endophthalmitis. |
| – Empiric therapy following open globe injury | Vancomycin 40 mg/kg/day IV div q8h AND cefepime 150 mg/kg/day IV div q8h (AIII) | |
| – Staphylococcal | Vancomycin 40 mg/kg/day IV div q8h pending susceptibility testing; oxacillin/nafcillin 150 mg/kg/day IV div q6h if susceptible (AIII) | |
| – Pneumococcal, meningococcal, *Haemophilus* | Ceftriaxone 100 mg/kg/day IV q24h; penicillin G 250,000 U/kg/day IV div q4h if susceptible (AIII) | Rule out meningitis; treatment course for 10–14 days. |
| – Gonococcal | Ceftriaxone 50 mg/kg q24h IV, IM (AIII) | Treatment course 7 days or longer |
| – *Pseudomonas* | Cefepime 150 mg/kg/day IV div q8h for 10–14 days (AIII) | Cefepime is preferred over ceftazidime for *Pseudomonas* based on decreased risk of development of resistance on therapy; meropenem IV or imipenem IV are alternatives (no clinical data). Very poor outcomes. |
| – *Candida* | Intravitreal amphotericin 5-10 μg/0.1 mL sterile water AND fluconazole 12 mg/kg/day IV (Load fluconazole with 25 mg/kg IV on day 1.) (AIII) | Echinocandins given IV may not be able to achieve adequate antifungal activity in the eye.[66] |

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| **Hordeolum (sty) or chalazion** | None (topical antibiotic not necessary) | Warm compresses; I&D when necessary |
| **Retinitis** | | |
| – CMV[67–69]<br>For neonatal: See Chapter 5. For HIV-infected children, visit NIH Web site at http://aidsinfo.nih.gov/guidelines/html/5/pediatric-oi-prevention-and-treatment-guidelines/0 | Ganciclovir 10 mg/kg/day IV div q12h for 2 wk (BIII); if needed, continue at 5 mg/kg/day q24h to complete 6 wk total (BIII) | Neutropenia risk increases with duration of therapy.<br>Foscarnet IV and cidofovir IV are alternatives but demonstrate significant toxicities.<br>Oral valganciclovir has not been evaluated in HIV-infected children with CMV retinitis but is an option primarily for older children who weigh enough to receive the adult dose of valganciclovir (CIII).<br>Intravitreal ganciclovir and combination therapy for non-responding, immunocompromised hosts. |

## D. EAR AND SINUS INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Bullous myringitis**<br>(See Otitis media, acute.) | Believed to be a clinical presentation of acute bacterial otitis media | |
| **Mastoiditis, acute**<br>(pneumococcus, *S aureus,* including CA-MRSA; group A streptococcus; increasing *Pseudomonas* in adolescents, *Haemophilus* rare)[70–72] | Cefotaxime 150 mg/kg/day IV div q8h or ceftriaxone 50 mg/kg/day q24h AND clindamycin 40 mg/kg/day IV div q8h (BIII)<br>For adolescents: cefepime 150 mg/kg/day IV div q8h AND clindamycin 40 mg/kg/day IV div q8h (BIII) | Rule out meningitis; surgery as needed for mastoid and middle ear drainage.<br>Change to appropriate oral therapy after clinical improvement. |
| **Mastoiditis, chronic**<br>(See also Otitis, chronic suppurative.) (anaerobes, *Pseudomonas, S aureus* [including CA-MRSA])[71] | Antibiotics only for acute superinfections (according to culture of drainage); for *Pseudomonas:* meropenem 60 mg/kg/day IV div q8h, OR pip/tazo 240 mg/kg/day IV div q4–6h for only 5-7 days after drainage stops (BIII) | Daily cleansing of ear important; if no response to antibiotics, surgery.<br>Alternatives: cefepime IV or ceftazidime IV (poor anaerobic coverage with either antibiotic).<br>Be alert for CA-MRSA. |

## D. EAR AND SINUS INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Otitis externa** | | |
| Bacterial, swimmer's ear (*P aeruginosa, S aureus,* including CA-MRSA)[73–76] | Topical antibiotics: fluoroquinolone (ciprofloxacin or ofloxacin) with steroid, OR neomycin/polymyxin B/hydrocortisone (BII)<br>Irrigation and cleaning canal of detritus important | Wick moistened with Burow solution, used for marked swelling of canal; to prevent swimmer's ear, 2% acetic acid to canal after water exposure will restore acid pH. |
| – Bacterial, malignant otitis externa (*P aeruginosa*)[75] | Cefepime 150 mg/kg/day IV div q8h (AIII) | Other antipseudomonal antibiotics should also be effective: ceftazidime IV AND tobramycin IV, OR meropenem IV or imipenem IV, pip/tazo IV.<br>For more mild infection, ciprofloxacin PO. |
| – Bacterial furuncle of canal (*S aureus,* including CA-MRSA) | Standard: oxacillin/nafcillin 150 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h (BIII)<br>CA-MRSA: clindamycin 30 mg/kg/day IV div q8h or vancomycin 40 mg/kg/day IV q8h (BIII) | I&D; antibiotics for cellulitis<br>Oral therapy for mild disease, convalescent therapy: for MSSA: cephalexin; for CA-MRSA: clindamycin, TMP/SMX, OR linezolid (BIII) |
| – *Candida* | Fluconazole 6–12 mg/kg/day PO qd for 5–7 days (CIII) | May occur following antibiotic therapy of bacterial external otitis; debride canal |
| **Otitis media, acute** | | |

**A note on AOM:** The natural history of AOM in different age groups by specific pathogens has not been well defined; therefore, the actual contribution of antibiotic therapy on resolution of disease has also been poorly defined until 2 recent amox/clav vs placebo, blinded, prospective studies were published,[77,78] although neither study required tympanocentesis to define a pathogen. The benefits and risks (including development of antibiotic resistance) of antibiotic therapy for AOM need to be further evaluated before the most accurate advice on the "best" antibiotic can be provided. However, based on available data, for most children, amoxicillin or amox/clav can be used initially. Considerations for the need for extended antimicrobial activity of amox/clav include severity of disease, young age of the child, previous antibiotic therapy within 6 months, and child care attendance, which address the issues of types of pathogens and antibiotic resistance patterns to expect. However, with universal PCV13 immunization, preliminary data suggest that the risk of antibiotic-resistant pneumococcal otitis has decreased but the percent of *Haemophilus* responsible for AOM has increased; therefore, some experts recommend the use of amox/clav as first-line therapy for well-documented AOM. The most current

AAP guidelines[79] and meta-analyses[80] suggest the greatest benefit with therapy occurs in children with bilateral AOM who are younger than 2 years; for other children, close observation is also an option. AAP guidelines provide an option to treatment in non-severe cases, particularly disease in older children, to provide a prescription to parents but have them only fill the prescription if the child deteriorates.[79] Although prophylaxis is only rarely indicated, amoxicillin or other antibiotics can be used in half the therapeutic dose once or twice daily to prevent infections if the benefits outweigh the risks of development of resistant organisms for that child.[79]

| | | |
|---|---|---|
| – Newborns | See Chapter 5. | |
| – Infants and children (pneumococcus, *H influenzae* non–type b, *Moraxella* most common)[81–83] | Usual therapy: amoxicillin 90 mg/kg/day PO div bid, with or without clavulanate; failures will be caused by highly pen-R pneumococcus or, if amoxicillin is used alone, by beta-lactamase–producing *Haemophilus* (or *Moraxella*).<br>a) For *Haemophilus* strains that are beta-lactamase positive, the following oral antibiotics offer better in vitro activity than amoxicillin: amox/clav, cefdinir, cefpodoxime, cefuroxime, ceftriaxone IM, levofloxacin.<br>b) For pen-R pneumococci: high-dosage amoxicillin achieves greater middle ear activity than oral cephalosporins. Options include ceftriaxone IM 50 mg/kg/day q24h for 1–3 doses; OR levofloxacin 20 mg/kg/day PO div bid for children $\leq$5 y and 10 mg/kg PO qd for children $>$5 y; OR a macrolide-class antibiotic*: azithromycin PO at 1 of 3 dosages: (1) 10 mg/kg on day 1, followed by 5 mg/kg qd on days 2–5; (2) 10 mg/kg qd for 3 days; or (3) 30 mg/kg once.<br>*Caution: Up to 40% of pen-R pneumococci are also macrolide resistant. | See Chapter 11 for dosages. Until published data document the lack of penicillin resistance in pneumococci isolated from infants with AOM in the post–13-valent pneumococcal conjugate vaccine era,[82] high-dosage amoxicillin (90 mg/kg/day) should still be used for empiric therapy. The high serum and middle ear fluid concentrations achieved with 45 mg/kg/dose of amoxicillin, combined with a long half-life in middle ear fluid, allow for a therapeutic antibiotic exposure in the middle ear with only twice-daily dosing; high-dose amoxicillin (90 mg/kg/day) with clavulanate (Augmentin ES) is also available. As published data document decreasing resistance to amoxicillin, standard dosage (45 mg/kg/day) can again be recommended.<br>Tympanocentesis should be performed in children who fail second-line therapy. |

## D. EAR AND SINUS INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Otitis, chronic suppurative** (*P aeruginosa, S aureus,* including CA-MRSA, and other respiratory tract/skin flora)[84,85] | Topical antibiotics: fluoroquinolone (ciprofloxacin, ofloxacin, besifloxacin) with or without steroid (BIII)<br>Cleaning of canal, view of tympanic membrane, for patency; cultures important | Presumed middle ear drainage through open tympanic membrane; possible aminoglycoside toxicity if neomycin-containing topical therapy used[86]<br>Other topical fluoroquinolones with/without steroids available |
| **Sinusitis, acute** (*H influenzae* non–type b, pneumococcus, group A streptococcus, *Moraxella*)[87–90] | Same antibiotic therapy as for AOM as pathogens similar: amoxicillin 90 mg/kg/day PO div bid, OR for children at higher risk of *Haemophilus,* amox/clav 14:1 ratio, with amoxicillin component at 90 mg/kg/day PO div bid (BIII).<br>Therapy of 14 days may be necessary while mucosal swelling resolves and ventilation is restored. | IDSA sinusitis guidelines recommend amox/clav as first-line therapy,[90] while AAP guidelines (same pediatric authors) recommend amoxicillin.[88] Lack of data prevents a definitive evidence-based recommendation. The same antibiotic therapy considerations used for AOM apply to acute bacterial sinusitis.<br>Sinus irrigations for severe disease or failure to respond. |

## E. OROPHARYNGEAL INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Dental abscess**[91,92] | Clindamycin 30 mg/kg/day PO, IV, IM div q6–8h OR penicillin G 100–200,000 U/kg/day IV div q6h (AIII) | Amox/clav PO; amoxicillin PO; ampicillin AND metronidazole IV are other options.<br>Tooth extraction usually necessary. Erosion of abscess may occur into facial, sinusitis, deep head, and neck compartments. |
| **Diphtheria**[93] | Erythromycin 40–50 mg/kg/day PO div qid for 14 days OR penicillin G 150,000 U/kg/day IV div q6h; PLUS antitoxin (AIII) | DAT, a horse antisera, is investigational and only available from CDC Emergency Operations Center at 770/488-7100. The investigational protocol and dosages of DAT are provided on the CDC Web site at www.cdc.gov/diphtheria/downloads/protocol.pdf (protocol version 3/26/14; accessed August 28, 2015). |
| **Epiglottitis** (aryepiglottitis, supraglottitis; *H influenzae* type b in an unimmunized child; rarely pneumococcus, *S aureus*)[94,95] | Ceftriaxone 50 mg/kg/day IV, IM q24h OR cefotaxime 150 mg/kg/day IV div q8h for 7–10 days | Emergency: provide airway.<br>For *S aureus* (causes only 5% of epiglottitis), consider adding clindamycin 40 mg/kg/day IV div q8h. |
| **Gingivostomatitis, herpetic**[96–98] | Acyclovir 80 mg/kg/day PO div qid for 7 days (for severe disease, use IV therapy at 30 mg/kg/day div q8h) (BIII); OR for infants ≥3 mo, valacyclovir 20 mg/kg/dose PO bid (instructions for preparing liquid formulation with 28-day shelf life included in package insert) (CIII)[98] | Early treatment is likely to be the most effective. Start treatment as soon as oral intake is compromised.<br>Extended duration of therapy may be needed for immunocompromised children.<br>This oral acyclovir dose is safe and effective for varicella; 75 mg/kg/day div into 5 equal doses has been studied for HSV.[97]<br>Limited pediatric valacyclovir pharmacokinetic data and preparation of an extemporaneous suspension are included in the valacyclovir FDA-approved package label.<br>Consider adding amox/clav or clindamycin for severe disease with oral flora superinfection. |

## E. OROPHARYNGEAL INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Lemierre syndrome** (*Fusobacterium necrophorum*)[99,100] (pharyngitis with internal jugular vein septic thrombosis, postanginal sepsis, necrobacillosis) | Empiric: meropenem 60 mg/kg/day div q8h (or 120 mg/kg/day div q8h for CNS metastatic foci) (AIII) OR ceftriaxone 100 mg/kg/day q24h AND metronidazole 40 mg/kg/day div q8h or clindamycin 40 mg/kg/day div q6h (BIII) | Anecdotal reports suggest metronidazole may be effective for apparent failures with other agents.<br>Often requires anticoagulation.<br>Metastatic and recurrent abscesses often develop while on active, appropriate therapy, requiring multiple debridements and prolonged antibiotic therapy. Treat until CRP and ESR are normal (AIII). |
| **Peritonsillar cellulitis or abscess** (group A streptococcus with mixed oral flora, including anaerobes, CA-MRSA)[101] | Clindamycin 30 mg/kg/day PO, IV, IM div q8h AND cefotaxime 150 mg/kg/day IV div q8h or ceftriaxone 50 mg/kg/day IV q24h (BIII) | Consider incision and drainage for abscess.<br>Alternatives: meropenem or imipenem; pip/tazo; amox/clav for convalescent oral therapy (BIII).<br>No useful data on benefits of steroids. |
| **Pharyngitis** (group A streptococcus) (tonsillopharyngitis)[7,102–104] | Amoxicillin 50–75 mg/kg/day PO, either qd, bid, or tid for 10 days OR penicillin V 50–75 mg/kg/day PO div bid or tid, OR benzathine penicillin 600,000 units IM for children <27 kg, 1.2 million units IM if >27 kg, as a single dose (AII)<br>For penicillin-allergic children: erythromycin (estolate at 20–40 mg/kg/day PO div bid to qid; or ethylsuccinate at 40 mg/kg/day PO div bid to qid) for 10 days; or azithromycin 12 mg/kg qd for 5 days (AII) | Amoxicillin displays better GI absorption than oral penicillin V; the suspension is better tolerated. These advantages should be balanced by the unnecessary increased spectrum of activity.<br>Once-daily amoxicillin dosage: for children 50 mg/kg (max 1,000–1,200 mg).[7]<br>Meta-analysis suggests that oral cephalosporins are more effective than penicillin for treatment of strep.[105]<br>Clindamycin is also effective.<br>A 5-day treatment course is FDA approved for some oral cephalosporins (cefdinir, cefpodoxime), with rapid clinical response to treatment that can be seen with other antibiotics; a 10-day course is preferred for the prevention of ARF, particularly areas where ARF is prevalent. No data exist on efficacy of 5 days of therapy for prevention of ARF.[104,106] |

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| **Retropharyngeal, parapharyngeal, or lateral pharyngeal cellulitis or abscess** (mixed aerobic/anaerobic flora, now including CA-MRSA)[101,107,108] | Clindamycin 40 mg/kg/day IV div q8h AND cefotaxime 150 mg/kg/day IV div q8h or ceftriaxone 50 mg/kg/day IV q24h | Consider I&D; possible airway compromise, mediastinitis.<br>Alternatives: meropenem or imipenem (BIII); pip/tazo; amox/clav for convalescent oral therapy (BIII). |
| **Tracheitis, bacterial** (*S aureus,* including CA-MRSA; group A streptococcus; pneumococcus; *H influenzae* type b, rarely *Pseudomonas*)[109,110] | Vancomycin 40 mg/kg/day IV div q8h or clindamycin 40 mg/kg/day IV div q8h AND ceftriaxone 50 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h | For susceptible *S aureus,* oxacillin/nafcillin or cefazolin<br>May represent bacterial superinfection of viral laryngotracheobronchitis, including influenza |

## F. LOWER RESPIRATORY TRACT INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Abscess, lung** | | |
| – Primary (severe, necrotizing community-acquired pneumonia caused by pneumococcus, *S aureus,* including CA-MRSA, group A streptococcus)[111,112] | Empiric therapy with ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h AND clindamycin 40 mg/kg/day div q8h or vancomycin 45 mg/kg/day IV div q8h for 14–21 days or longer (AIII) | For severe CA-MRSA infections, see Chapter 4.<br>Bronchoscopy may be necessary if abscess fails to drain; surgical excision rarely necessary for pneumococcus but more important for CA-MRSA and MSSA.<br>Focus antibiotic coverage based on culture results.<br>For MSSA: oxacillin/nafcillin or cefazolin. |
| – Secondary to aspiration (ie, foul smelling; polymicrobial infection with oral aerobes and anaerobes)[113] | Clindamycin 40 mg/kg/day IV div q8h or meropenem 60 mg/kg/day IV div q8h for 10 days or longer (AIII) | Alternatives: imipenem IV or pip/tazo IV or ticar/clav IV (BIII)<br>Oral step-down therapy with clindamycin or amox/clav (BIII) |
| **Allergic bronchopulmonary aspergillosis**[114] | Prednisone 0.5 mg/kg qod (BII) AND voriconazole 18 mg/kg/day PO div q12h load followed by 16 mg/kg/day div q12h (AIII) OR itraconazole 10 mg/kg/day PO div q12h (BII) | Larger steroid dosages may lead to tissue invasion by *Aspergillus.*<br>Voriconazole not as well studied in allergic bronchopulmonary aspergillosis but is more active than itraconazole.<br>Voriconazole or itraconazole require trough concentration monitoring. |
| **Aspiration pneumonia** (polymicrobial infection with oral aerobes and anaerobes)[113] | Clindamycin 40 mg/kg/day IV div q8h; ADD ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h for additional *Haemophilus* activity OR meropenem 60 mg/kg/day IV div q8h; for 10 days or longer (BIII) | Alternatives: imipenem IV or pip/tazo IV or ticar/clav IV (BIII)<br>Oral step-down therapy with clindamycin or amox/clav (BIII) |
| **Atypical pneumonia** (See *M pneumoniae,* Legionnaires disease.) | | |

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|---|---|---|
| **Bronchitis** (bronchiolitis), acute[115] | For bronchitis/bronchiolitis in children, no antibiotic needed for most cases, as disease is usually viral | |
| **Community-acquired pneumonia** (See Pneumonia: Community-acquired, bronchopneumonia; Pneumonia: Community-acquired, lobar consolidation.) | | |
| **Cystic fibrosis:** Seek advice from those expert in acute and chronic management. | | |
| – Acute exacerbation (*P aeruginosa* primarily; also *Burkholderia cepacia, Stenotrophomonas maltophilia, S aureus,* including CA-MRSA, nontuberculous mycobacteria)[116–120] | Ceftazidime 150–200 mg/kg/day div q6–8h or meropenem 120 mg/kg/day div q6h AND tobramycin 6–10 mg/kg/day IM, IV div q6–8h for treatment of acute infection (AII); alternatives: imipenem, cefepime, or ciprofloxacin 30 mg/kg/day PO, IV div tid<br>May require vancomycin 60–80 mg/kg/day IV div q8h for MRSA<br>Duration of therapy not well defined: 10–14 days (BIII)[117] | Larger than normal dosages of antibiotics required in most patients with cystic fibrosis due to increased clearance; monitor concentrations of aminoglycosides, vancomycin.<br>Insufficient evidence to recommend routine use of inhaled antibiotics for acute exascerbations.[121]<br>Cultures with susceptibility testing and synergy testing will help select antibiotics, as multidrug resistance is common, but synergy testing not well standardized.[122,123]<br>Combination therapy may provide synergistic killing and delay the emergence of resistance (BIII).<br>Attempt at early eradication of new onset *Pseudomonas* may decrease progression of disease.[119]<br>Failure to respond to antibacterials should prompt evaluation for allergic fungal disease. |
| Chronic inflammation (Minimize long-term damage to lung.) | Inhaled tobramycin 300 mg bid, cycling 28 days on therapy, 28 days off therapy, is effective adjunctive therapy between exacerbation[124] (AI).<br>Inhaled aztreonam[125] provides an alternative to inhaled tobramycin (AI).<br>Azithromycin adjunctive chronic therapy, greatest benefit for those colonized with *Pseudomonas* (AII).[126,127] | Alternative inhaled antibiotics: aztreonam[127]; colistin[121,128] (BIII)<br>Two new powder preparations of inhaled tobramycin now available |

## F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Pertussis**[129,130] | Azithromycin 10 mg/kg/day for 5 days, or clarithromycin 15 mg/kg/day div bid for 7 days, or erythromycin (estolate preferable) 40 mg/kg/day PO div qid; for 7–10 days (AII)<br>Alternative: TMP/SMX 8 mg/kg/day TMP div bid for 10 days (BIII) | Azithromycin and clarithromycin are better tolerated than erythromycin; azithromycin is preferred in young infants to reduce pyloric stenosis risk (see Chapter 5).<br>The azithromycin dosage that is recommended for very young neonates with the highest risk of mortality (<1 mo) is 10 mg/kg/day for 5 days. This dose should be used up to 6 mo of age. Older children should receive 10 mg/kg on day 1, followed by 5 mg/kg on days 2–5.[129] Provide prophylaxis to family members. |
| **Pneumonia: Community-acquired, bronchopneumonia** | | |
| – Mild to moderate illness (overwhelmingly viral, especially in preschool children)[131] | No antibiotic therapy unless epidemiologic, clinical, or laboratory reasons to suspect bacteria or *Mycoplasma* | Broad-spectrum antibiotics may increase risk of subsequent infection with antibiotic-resistant pathogens. |
| – Moderate to severe illness (pneumococcus; group A streptococcus; *S aureus,* including CA-MRSA; or *Mycoplasma pneumoniae*[111,112,132–134]; and for those with aspiration due to underlying comorbidities, *Haemophilus influenzae,* nontypable) | Empiric therapy:<br>For regions with high PCV13 vaccine use or low pneumococcal resistance to penicillin: ampicillin 200 mg/kg/day div q6h.<br>For regions with low rates of PCV13 use or high pneumococcal resistance to penicillin: ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h (AI).<br>For suspected CA-MRSA, use vancomycin 40–60 mg/kg/day (AIII).[2]<br>For suspect *Mycoplasma*/atypical pneumonia agents, particularly in school-aged children, ADD azithromycin 10 mg/kg IV, PO on day 1, then 5 mg/kg qd for days 2–5 of treatment (AII). | Tracheal aspirate or bronchoalveolar lavage for Gram stain/culture for severe infection in intubated children.<br>Check vancomycin serum concentrations and renal function, particularly at the higher dosage needed to achieve an AUC:MIC of 400 for CA-MRSA pneumonia.<br>Alternatives to azithromycin for atypical pneumonia include erythromycin IV, PO, or clarithromycin PO, or doxycycline IV, PO for children >7 y, or levofloxacin for postpubertal older children.<br>New data suggest that combination empiric therapy with a beta-lactam and a macrolide results in shorter hospitalization compared with a beta-lactam alone, but we are not ready to recommend routine empiric combination therapy yet.[135] |

| Pneumonia: Community-acquired, lobar consolidation | | |
|---|---|---|
| **Pneumococcus**<br>(May occur with nonvaccine strains, even if immunized for pneumococcus.[111,112,132–134])<br>Consider *H influenzae* type b in the unimmunized child.<br>(*M pneumoniae* may cause lobar pneumonia.) | Empiric therapy:<br>For regions with high PCV13 vaccine use or low pneumococcal resistance to penicillin: ampicillin 200 mg/kg/day div q6h.<br>For regions with low rates of PCV13 use or high pneumococcal resistance to penicillin: ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h (AI); for more severe disease ADD clindamycin 40 mg/kg/day div q8h or vancomycin 40–60 mg/kg/day div q8h for suspect *S aureus* (AIII).[2]<br>For suspect *Mycoplasma*/atypical pneumonia agents, particularly in school-aged children, ADD azithromycin 10 mg/kg IV, PO on day 1, then 5 mg/kg qd for days 2–5 of treatment (AII).<br>Empiric oral outpatient therapy for less severe illness: high-dosage amoxicillin 80–100 mg/kg/day PO div q8h (NOT q12h); for *Mycoplasma,* ADD a macrolide as above (BIII). | Change to PO after improvement (decreased fever, no oxygen needed); treat until clinically asymptomatic and chest radiography significantly improved (7–21 days) (BIII).<br>No reported failures of ceftriaxone/cefotaxime for pen-R pneumococcus; no need to add empiric vancomycin for this reason (CIII).<br>Oral therapy for pneumococcus and *Haemophilus* may also be successful with amox/clav, cefdinir, cefixime, cefpodoxime, or cefuroxime.<br>Levofloxacin is an alternative, particularly for those with severe allergy to beta-lactam antibiotics (BI),[136] but, due to theoretical cartilage toxicity concerns, should not be first-line therapy. |
| – Pneumococcal, pen-S | Penicillin G 250,000–400,000 U/kg/day IV div q4–6h for 10 days (BII) or ampicillin 200 mg/kg/day IV divided q6h | After improvement, change to PO amoxicillin 50–75 mg/kg/day PO div tid, or penicillin V 50–75 mg/kg/day div qid. |
| – Pneumococcal, pen-R | Ceftriaxone 75 mg/kg/day q24h, or cefotaxime 150 mg/kg/day div q8h for 10–14 days (BIII) | Addition of vancomycin has not been required for eradication of pen-R strains.<br>For oral convalescent therapy, high-dosage amoxicillin (100–150 mg/kg/day PO div tid), clindamycin (30 mg/kg/day PO div tid), linezolid (30 mg/kg/day PO div tid), or levofloxacin PO. |

## F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| ***S aureus*** (including CA-MRSA)[2,6,111,132,137] | For MSSA: oxacillin/nafcillin 150 mg/kg/day IV div q6h or cefazolin 100 mg/kg/day IV div q8h (AII)<br>For CA-MRSA: vancomycin 60 mg/kg/day; may need addition of rifampin, clindamycin, or gentamicin (AIII) (See Chapter 4.) | Check vancomycin serum concentrations and renal function, particularly at the higher dosage designed to attain an AUC:MIC of 400, or serum trough concentrations of 15 µg/mL for invasive CA-MRSA disease.<br>For life-threatening disease, optimal therapy of CA-MRSA is not defined: add gentamicin and/or rifampin.<br>Linezolid 30 mg/kg/day IV, PO div q8h is another option, more effective in adults than vancomycin for MRSA nosocomial pneumonia[138] (follow platelets and WBC weekly). |
| **Pneumonia: Immunosuppressed, neutropenic host**[139] (*P aeruginosa,* other community-associated or nosocomial gram-negative bacilli, *S aureus,* fungi, AFB, *Pneumocystis,* viral [adenovirus, CMV, EBV, influenza, RSV, others]) | Cefepime 150 mg/kg/day IV div q8h and tobramycin 6.0–7.5 mg/kg/day IM, IV div q8h (AII), OR meropenem 60 mg/kg/day div q8h (AII) ± tobramycin (BIII); AND if *S aureus* (including MRSA) is suspected clinically, ADD vancomycin 40–60 mg/kg/day IV div q8h (AIII). | Biopsy or bronchoalveolar lavage usually needed to determine need for antifungal, antiviral, antimycobacterial treatment. Antifungal therapy usually started if no response to antibiotics in 48–72 h (AmB, voriconazole, or caspofungin/micafungin — see Chapter 8).<br>Amikacin 15–22.5 mg/kg/day is an alternative aminoglycoside.<br>Use 2 active agents for definitive therapy for compromised hosts, as neutrophils cannot assist clearing the pathogen; may also decrease risk of emergence of resistance (BIII). |
| – **Pneumonia: Interstitial pneumonia syndrome of early infancy** | If *Chlamydia trachomatis* suspected, azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day qd days 2–5 OR erythromycin 40 mg/kg/day PO div qid for 14 days (BII) | Most often respiratory viral pathogens, CMV, or chlamydial; role of *Ureaplasma* uncertain |
| – **Pneumonia, nosocomial (health care–associated/ventilator-associated)** (*P aeruginosa,* gram-negative enteric bacilli [*Enterobacter, Klebsiella, Serratia, Escherichia coli*], *Acinetobacter,* | Commonly used regimens:<br>Meropenem 60 mg/kg/day div q8h, OR pip/tazo 240–300 mg/kg/day div q6–8h, OR cefepime 150 mg/kg/day div q8h; ± gentamicin 6.0–7.5 mg/kg/day div q8h (AIII); ADD vancomycin 40–60 mg/kg/day div q8h for suspect CA-MRSA (AIII). | Empiric therapy should be institution specific, based on your hospital's nosocomial pathogens and susceptibilities. Pathogens that cause nosocomial pneumonia often have multidrug resistance. Cultures are critical. Empiric therapy also based on child's prior colonization/infection.<br>For multidrug-resistant gram-negative bacilli, colistin IV may be required. |

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| *Stenotrophomonas,* and gram-positive organisms including CA-MRSA and *Enterococcus*)[140–143] | | Aminoglycosides may not achieve therapeutic concentrations in ELF.[143]<br>Aerosol delivery of antibiotics may be required for multidrug-resistant pathogens.[144] |
| – **Pneumonia: With pleural fluid/empyema** (same pathogens as for community-associated bronchopneumonia) (Based on extent of fluid and symptoms, may benefit from chest tube drainage with fibrinolysis or video-assisted thoracoscopic surgery[132,145–148]) | Empiric therapy: ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h AND vancomycin 40–60 mg/kg/day IV div q8h (BIII) | Initial therapy based on Gram stain of empyema fluid; typically clinical improvement is slow, with persisting but decreasing "spiking" fever for 2–3 wk. |
| – Group A streptococcal | Penicillin G 250,000 U/kg/day IV div q4–6h for 10 days (BII) | Change to PO amoxicillin 75 mg/kg/day div tid or penicillin V 50–75 mg/kg/day div qid to tid after clinical improvement (BIII). |
| – Pneumococcal | (See Pneumonia: Community-acquired, lobar consolidation.) | |
| *S aureus* (including CA-MRSA)[2,6,111,137] | For MSSA: oxacillin/nafcillin or cefazolin (AII).<br>For CA-MRSA: use vancomycin 60 mg/kg/day (AIII) (designed to attain an AUC:MIC of 400, or serum trough concentrations of 15 µg/mL); follow serum concentrations and renal function; may need additional antibiotics (see Chapter 4). | For life-threatening disease, optimal therapy of CA-MRSA is not defined: add gentamicin and/or rifampin.<br>Oral convalescent therapy for MSSA: cephalexin PO; for CA-MRSA: clindamycin or linezolid PO.<br>Total course for 21 days or longer (AIII).<br>For children infected who do not tolerate high-dose vancomycin, alternatives include clindamycin, linezolid, and ceftaroline. |

## F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Pneumonias of other established etiologies** (See Chapter 7 for treatment by pathogen.) | | |
| – *Chlamydophila*[149] (formerly *Chlamydia*) *pneumoniae, C psittaci,* or *C trachomatis* | Azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day qd days 2–5 or erythromycin 40 mg/kg/day PO div qid; for 14 days | Doxycycline (patients >7 y) |
| – CMV (immunocompromised host)[150,151] (See chapters 5 and 9 for CMV infection in newborns.) | Ganciclovir IV 10 mg/kg/day IV div q12h for 2 wk (BIII); if needed, continue at 5 mg/kg/day q24h to complete 4–6 wk total (BIII). | Add CMV immune globulin to provide a small incremental benefit in bone marrow transplant patients (BII).<br>Oral valganciclovir may be used for convalescent therapy (BIII).<br>Foscarnet for ganciclovir-resistant strains. |
| – *E coli* | Ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h (AII) | For cephalosporin-resistant strains (ESBL producers), use meropenem, imipenem, or ertapenem (AIII). |
| – *Enterobacter* spp | Cefepime 100 mg/kg/day div q12h or meropenem 60 mg/kg/day div q8h; OR ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h AND gentamicin 6.0–7.5 mg/kg/day IM, IV div q8h (AIII) | Addition of aminoglycoside to 3rd-generation cephalosporins may retard the emergence of ampC-mediated constitutive high-level resistance, but concern exists for inadequate aminoglycoside concentration in airways[147]; not needed with cefepime, meropenem, or imipenem. |
| – *Francisella tularensis*[152] | Gentamicin 6.0–7.5 mg/kg/day IM, IV div q8h for 10 days or longer for more severe disease (AIII); for less severe disease, doxycycline PO for 14–21 days (AIII) | Alternatives for oral therapy of mild disease: ciprofloxacin or levofloxacin (BIII) |
| – Fungi (See Chapter 8.)<br>– Community-associated pathogens, vary by region (eg, *Coccidioides*,[153,154] *Histoplasma*[155,156]) | For pathogen-specific recommendations, see Chapter 8.<br>For suspected endemic fungi or mucormycosis in immunocompromised host, treat empirically with a lipid AmB and not voriconazole; biopsy needed to guide therapy. | For normal hosts, triazoles (fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole) are better tolerated than AmB and equally effective for many community-associated pathogens (see Chapter 2). For dosage, see Chapter 8.<br>Check voriconazole trough concentrations; need to be at least >2 µg/mL. |

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| – *Aspergillus,* mucormycosis, other mold infections in immunocompromised hosts[143] | For suspected invasive aspergillosis, treat with voriconazole (AI) (load 18 mg/kg/day div q12h on day 1, then continue 16 mg/kg/day div q12h). | For refractory *Coccidioides* infection, combination therapy with voriconazole and caspofungin may be effective[153] (AIII). |
| – Influenza virus[157,158]<br>– Recent seasonal influenza A and influenza B strains continue to be resistant to adamantanes. | Empiric therapy, or documented influenza A or influenza B:<br>Oseltamivir[158,159] (AII):<br><12 mo:<br>Term infants 0–8 mo: 3 mg/kg/dose bid<br>9–11 mo: 3.5 mg/kg/dose bid<br>≥12 mo:<br>≤15 kg: 30 mg PO bid<br>>15–23 kg: 45 mg PO bid<br>>23–40 kg: 60 mg PO bid<br>>40 kg: 75 mg PO bid<br>Zanamivir inhaled (AII): for those ≥7 y 10 mg (two 5-mg inhalations) bid | Check for antiviral susceptibility each season at www.cdc.gov/flu/professionals/antivirals/index.htm (accessed August 28, 2015).<br>For children 12–23 mo, the unit dose of 30 mg/dose may provide inadequate drug exposure. 3.5 mg/kg/dose PO bid has been studied,[159] but sample sizes have been inadequate to recommend weight-based dosing at this time.<br>The adamantanes (amantadine and rimantadine) had activity against influenza A prior to the late 1990s, but all circulating A strains of influenza have been resistant for many years. Influenza B is intrinsically resistant to adamantanes.<br>Limited data for premature neonates[158]:<br><38 wk postmenstrual age (gestational plus chronologic age): 1.0 mg/kg/dose, PO bid<br>38–40 wk postmenstrual age: 1.5 mg/kg/dose, PO bid |
| – *Klebsiella pneumoniae*[160,161] | Ceftriaxone 50–75 mg/kg/day IV, IM q24h OR cefotaxime 150 mg/kg/day IV, IM div q8h (AIII); for ceftriaxone-resistant strains (ESBL strains), use meropenem 60 mg/kg/day IV div q8h (AIII) or other carbapenem. | For *K pneumoniae* carbapenemase-producing strains that are resistant to meropenem: alternatives include ceftazidime/avibactam (FDA-approved for adults, pediatric studies in progress), fluoroquinolones, or colistin (BIII). |
| – Legionnaires disease (*Legionella pneumophila*) | Azithromycin 10 mg/kg IV, PO q24h for 5 days (AIII) | Alternatives: clarithromycin, erythromycin, ciprofloxacin, levofloxacin, doxycycline |
| – Mycobacteria, nontuberculous (*M avium* complex most common)[11] | In a normal host: azithromycin PO or clarithromycin PO for 6–12 wk if susceptible<br>For more extensive disease: a macrolide AND rifampin AND ethambutol; ± amikacin or streptomycin (AIII) | Highly variable susceptibilities of different nontuberculous mycobacterial species<br>Check if immunocompromised: HIV or gamma-interferon receptor deficiency |

## F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – *Mycobacterium tuberculosis* (See Tuberculosis.) | | |
| – *M pneumoniae*[132,162] | Azithromycin 10 mg/kg on day 1, followed by 5 mg/kg/day qd days 2–5, or clarithromycin 15 mg/kg/day div bid for 7–14 days, or erythromycin 40 mg/kg/day PO div qid for 14 days | *Mycoplasma* often causes self-limited infection and does not require treatment (AIII). Little prospective, well-controlled data exist for treatment of documented mycoplasma pneumonia specifically in children.[162]<br>Doxycycline (patients >7 y).<br>Macrolide-resistant strains have recently appeared worldwide.[163] |
| – *Paragonimus westermani* | See Chapter 10. | |
| – *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*)[164]; disease in immunosuppressed children and those with HIV | Severe disease: preferred regimen is TMP/SMX, 15–20 mg TMP component/kg/day IV div q8h for 3 wk (AI).<br>Mild-moderate disease: may start with IV therapy, then after acute pneumonitis is resolving, TMP/SMX 20 mg of TMP/kg/day PO div qid for 21 days (AII).<br>Use steroid adjunctive treatment for more severe disease (AII). | Alternatives for TMP/SMX intolerant, or clinical failure: pentamidine 3–4 mg IV qd, infused over 60–90 min (AII); TMP AND dapsone; OR primaquine AND clindamycin; OR atovaquone.<br>Prophylaxis: TMP/SMX as 5 mg TMP/kg/day PO, divided in 2 doses, q12h, daily or 3 times/wk on consecutive days (AI); OR TMP/SMX 5 mg TMP/kg/day PO as a single dose, once daily, given 3 times/wk on consecutive days (AI); once-weekly regimens have also been successful[165]; OR dapsone 2 mg/kg (max 100 mg) PO once daily, or 4 mg/kg (max 200 mg) once weekly; OR atovaquone: 30 mg/kg/day for infants 1–3 mo, 45 mg/kg/day for infants 4–24 mo, and 30 mg/kg/day for infants >24 mo. |
| – *P aeruginosa*[144,147,166,167] | Cefepime 150 mg/kg/day IV div q8h ± tobramycin 6.0–7.5 mg/kg/day IM, IV div q8h (AII). Alternatives: meropenem 60 mg/kg/day div q8h, OR pip/tazo 240–300 mg/kg/day div q6–8h (AII) ± tobramycin (BIII). | Ciprofloxacin IV, or colistin IV for multidrug-resistant strains |

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|---|---|---|
| RSV infection (bronchiolitis, pneumonia)[168] | For immunocompromised hosts, the only FDA-approved treatment is ribavirin aerosol: 6-g vial (20 mg/mL in sterile water), by SPAG-2 generator, over 18–20 h daily for 3–5 days.<br>Two antivirals are currently under investigation in children. | Treat only for severe disease, immunocompromised, severe underlying cardiopulmonary disease, as aerosol ribavirin only provides a small benefit. Airway reactivity with inhalation precludes routine use.<br>Ribavirin may also be given systemically (PO or IV) but has not been systematically evaluated for RSV.<br>Palivizumab (Synagis) is not effective for treatment of an active RSV infection, only effective for prevention of hospitalization in high-risk patients. |
| **Tuberculosis** | | |
| – Primary pulmonary disease[13,14] | INH 10–15 mg/kg/day (max 300 mg) PO qd for 6 mo AND rifampin 10–20 mg/kg/day (max 600 mg) PO qd for 6 mo AND PZA 30–40 mg/kg/day PO qd for first 2 mo therapy only (AII).<br>If risk factors present for multidrug resistance, add ethambutol 20 mg/kg/day PO qd OR streptomycin 30 mg/kg/day IV, IM div q12h initially. | Contact TB specialist for therapy of drug-resistant TB. Fluoroquinolones may play a role in treating multidrug-resistant strains. Bedaquiline, in a new drug class for TB therapy, was recently approved for adults with multidrug-resistant TB, when used in combination therapy. Toxicities and lack of pediatric data preclude routine use in children. Directly observed therapy preferred; after 2 wk of daily therapy, can change to twice-weekly dosing double dosage of INH (max 900 mg), PZA (max 2 g), and ethambutol (max 2.5 g); rifampin remains same dosage (10–20 mg/kg/day, max 600 mg) (AII).<br>LP ± CT of head for children ≤2 y to rule out occult, concurrent CNS infection; consider testing for HIV infection (AIII).<br>*Mycobacterium bovis* from unpasteurized dairy products can rarely cause pulmonary disease; also called "tuberculosis," but all strains of *M bovis* are PZA resistant. |

## F. LOWER RESPIRATORY TRACT INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – Latent TB infection[14] (skin test conversion) | INH 10–15 mg/kg/day (max 300 mg) PO daily for 9 mo (12 mo for immunocompromised patients) (AIII); treatment with INH at 20–30 mg/kg twice weekly for 9 mo is also effective (AIII).<br>Alternative[169] (BII): For children ≥2 y, once-weekly DOT for 12 weeks: INH (15 mg/kg/dose, max 900 mg), AND rifapentine:<br>10.0–14.0 kg: 300 mg<br>14.1–25.0 kg: 450 mg<br>25.1–32.0 kg: 600 mg<br>32.1–49.9 kg: 750 mg<br>≥50.0 kg: 900 mg (max) | Obtain baseline LFTs. Consider monthly LFTs or as needed for symptoms. Stop INH-rifapentine if AST or ALT ≥5 times the ULN even in the absence of symptoms or ≥3 times the ULN in the presence of symptoms.<br>For children ≥2–12 years, 12 wk of INH and rifapentine may be used, but less data on safety and efficacy.<br>Insufficient data for children <2 y.<br>For exposure to known INH-R but rifampin-S strains, use rifampin 6 mo (AIII). |
| – Exposed infant <4 y, or immunocompromised patient (high risk of dissemination) | INH 10–15 mg/kg PO daily for 2–3 mo after last exposure with repeat skin test or interferon-gamma release assay test negative (AIII) | If PPD remains negative at 2–3 mo and child well, consider stopping empiric therapy. PPD may not be reliable in immunocompromised patients. Not much data to assess reliability of interferon-gamma release assays in very young infants or immunocompromised hosts, but not likely to be much better than the PPD skin test. |

## G. CARDIOVASCULAR INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Bacteremia** | | |
| – Occult bacteremia (late-onset neonatal sepsis; fever without focus), infants <2 mo (group B streptococcus, *E coli, Listeria,* pneumococcus, meningococcus)[170–174] | In general, hospitalization for late-onset neonatal sepsis, with cultures of blood, urine, and CSF; start ampicillin 200 mg/kg/day IV div q6h AND cefotaxime 150 mg/kg/day IV div q8h (AII); higher dosages if meningitis is documented. | Current data document the importance of ampicillin-resistant *E coli* in bacteremia in infants <90 days.[172,173,175]<br>For a nontoxic, febrile infant with good access to medical care: cultures may be obtained of blood, urine, and CSF, ceftriaxone 50 mg/kg IM (lacks *Listeria* activity) given with outpatient follow-up the next day (Boston criteria) (BII); alternative is home without antibiotics if evaluation is negative (Rochester; Philadelphia criteria)[170,174] (BI). |
| – Occult bacteremia (fever without focus) in ages 2–3 mo to 36 mo (*H influenzae,* pneumococcus, meningococcus; increasingly *S aureus*)[173–175] | Empiric therapy: If unimmunized, febrile, mild-moderate toxic: after blood culture: ceftriaxone 50 mg/kg IM (BII).<br>If fully immunized (*Haemophilus* and *Pneumococcus*) and nontoxic, no routine antibiotic therapy recommended, but follow closely in case of vaccine failure or meningococcal bacteremia (BIII). | Oral convalescent therapy is selected by susceptibility of blood isolate, following response to IM/IV treatment, with CNS and other foci ruled out by examination ± laboratory tests ± imaging. |
| – *H influenzae* type b, non-CNS infections | Ceftriaxone IM/IV OR, if beta-lactamase negative, ampicillin IV, followed by oral convalescent therapy (AII) | If beta-lactamase negative: amoxicillin 75–100 mg/kg/day PO div tid (AII)<br>If positive: high-dosage cefixime, ceftibuten, cefdinir PO, or levofloxacin PO (CIII) |
| – Meningococcus | Ceftriaxone IM/IV or penicillin G IV, followed by oral convalescent therapy (AII) | Amoxicillin 75–100 mg/kg/day PO div tid (AIII) |

## G. CARDIOVASCULAR INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – Pneumococcus, non-CNS infections | Ceftriaxone IM/IV or penicillin G IV (if pen-S), followed by oral convalescent therapy (AII) | If pen-S: amoxicillin 75–100 mg/kg/day PO div tid (AII).<br>If pen-R: continue ceftriaxone IM, or switch to clindamycin if susceptible (CIII); linezolid or levofloxacin may also be options (CIII). |
| – *S aureus*[2,6,176–179] usually associated with focal infection | MSSA: nafcillin or oxacillin/nafcillin IV 150–200 mg/kg/day div q6h ± gentamicin 6 mg/kg/day div q8h (AII).<br>MRSA: vancomycin 40–60 mg/kg/day IV div q8h ± gentamicin 6 mg/kg/day div q8h ± rifampin 20 mg/kg/day div q12h. (AIII)<br>Treat for 2 wk (IV plus PO) from negative blood cultures unless endocarditis/endovascular thrombus present, which may require 6 wk of therapy (BIII). | For persisting bacteremia caused by MRSA, consider adding gentamicin, or changing from vancomycin to daptomycin 6–8 mg/kg qd (but will not treat pneumonia) or ceftaroline, particularly for MRSA with vancomycin MIC of >2 µg/mL.<br>For toxic shock syndrome, clindamycin should be added for the initial 48–72 h of therapy to decrease toxin production (linezolid may also act in this way); IVIG may be added to bind circulating toxin (linezolid may also act in this way); no controlled data exist for these measures.<br>Watch for the development of metastatic foci of infection, including endocarditis.<br>If catheter-related, remove catheter. |
| **Endocarditis:** Surgical indications: intractable heart failure; persistent infection; large mobile vegetations; peripheral embolism; and valve dehiscence, perforation, rupture or fistula, or a large perivalvular abscess[180–182] | | |
| – **Native valve**[180,181] | | |
| – Empiric therapy for presumed endocarditis (viridans streptococci, *Staphylococcus aureus*, HACEK group) | Ceftriaxone IV 100 mg/kg q24h AND gentamicin IV, IM 6 mg/kg/day div q8h (AII).<br>For severe infection, ADD vancomycin 40–60 mg/kg/day IV div q8h to cover *S aureus* (AIII). | Combination (ceftriaxone + gentamicin) provides bactericidal activity against most strains of viridans streptococci, the most common pathogens in infective endocarditis.<br>May administer gentamicin with a qd regimen (CIII).<br>For beta-lactam allergy, use vancomycin 45 mg/kg/day IV div q8h AND gentamicin 6 mg/kg/day IV div q8h. |
| – Viridans streptococci: Follow echocardiogram for resolution of vegetation (BIII); for beta-lactam allergy: vancomycin. | | |

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|---|---|---|
| Fully susceptible to penicillin | Ceftriaxone 50 mg/kg IV, IM q24h for 4 wk OR penicillin G 200,000 U/kg/day IV div q4–6h for 4 wk (BII); OR penicillin G or ceftriaxone AND gentamicin 6 mg/kg/day IM, IV div q8h for 14 days (AII) | |
| Relatively resistant to penicillin | Penicillin G 300,000 U/kg/day IV div q4–6h for 4 wk, or ceftriaxone 100 mg/kg IV q24h for 4 wk; AND gentamicin 6 mg/kg/day IM, IV div q8h for 2 wk (AIII) | Gentamicin is used for the first 2 wk of a total of 4 wk of therapy for relatively resistant strains. |
| – Enterococcus (dosages for native or prosthetic valve infections) | | |
| Ampicillin-susceptible (gentamicin-S)<br>Ampicillin-resistant (gentamicin-S)<br>Vancomycin-resistant (gentamicin-S) | Ampicillin 300 mg/kg/day IV, IM div q6h or penicillin G 300,000 U/kg/day IV div q4–6h; AND gentamicin 6.0 mg/kg/day IV div q8h; for 4–6 wk (AII)<br>Vancomycin 40 mg/kg/day IV div q8h AND gentamicin 6.0 mg/kg/day IV div q8h; for 4–6 wk (AIII)<br>Daptomycin IV (dose is age-dependent; see Chapter 11) AND gentamicin 6.0 mg/kg/day IV div q8h; for 4–6 wk (AIII) | Combined treatment with cell-wall active antibiotic plus aminoglycoside used to achieve bactericidal activity.<br>For beta-lactam allergy: vancomycin.<br>Little data exist in children for daptomycin, linezolid, or quinupristin/dalfopristin.<br>For gentamicin-R strains, use streptomycin or other aminoglycoside if susceptible. |
| – Staphylococci: *S aureus,* including CA-MRSA; *S epidermidis*[6,177] Consider continuing therapy at end of 6 wk if vegetations persist on echocardiogram. | MSSA or MSSE: nafcillin or oxacillin/nafcillin 150–200 mg/kg/day IV div q6h for 6 wk AND gentamicin 6 mg/kg/day div q8h for 14 days<br>CA-MRSA or MRSE: vancomycin 40–60 mg/kg/day IV div q8h AND gentamicin; ADD rifampin 20 mg/kg/day IV div q8–12h | Surgery may be necessary in acute phase; avoid first-generation cephalosporins (conflicting data on efficacy).<br>For failures on therapy, consider daptomycin (dose is age-dependent; see Chapter 11) AND gentamicin 6 mg/kg/day div q8h. |
| – Pneumococcus, gonococcus, group A streptococcus | Penicillin G 200,000 U/kg/day IV div q4–6h for 4 wk; alternatives: ceftriaxone or vancomycin | Ceftriaxone plus azithromycin for suspected gonococcus until susceptibilities known.<br>For penicillin non-susceptible strains of pneumococcus, use high-dosage penicillin G 300,000 U/kg/day IV div q4–6h or high-dosage ceftriaxone 100 mg/kg IV q24h for 4 wk. |

## G. CARDIOVASCULAR INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – **Prosthetic valve/material**[180,181] | | |
| – Viridans streptococci | | Follow echocardiogram for resolution of vegetation.<br>For beta-lactam allergy: vancomycin. |
| Fully susceptible to penicillin | Ceftriaxone 100 mg/kg IV, IM q24h for 6 wk OR penicillin G 300,000 U/kg/day IV div q4–6h for 6 wk (AII); OR penicillin G or ceftriaxone AND gentamicin 6.0 mg/kg/day IM, IV div q8h for first 2 wk of 6 wk course (AII) | Gentamicin is optional for the first 2 wk of a total of 6 wk of therapy for prosthetic valve/material endocarditis. |
| Relatively resistant to penicillin | Penicillin G 300,000 U/kg/day IV div q4–6h for 6 wk, or ceftriaxone 100 mg/kg IV q24h for 6 wk; AND gentamicin 6.0 mg/kg/day IM, IV div q8h for 6 wk (AIII) | Gentamicin is used for all 6 wk of therapy for prosthetic valve/material endocarditis caused by relatively resistant strains. |
| – Enterococcus (See dosages under native valve.) | | |
| – Staphylococci: *S aureus,* including CA-MRSA; *S epidermidis* (See dosages under native valve.) | | |
| – *Candida* | Caspofungin 70 mg/m$^2$ load on day 1, then 50 mg/m$^2$/day OR micafungin 2–4 mg/kg/day (BIII) | Fluconazole is known to not sterile cardiac vegetations well, and AmB products are also not ideal; echinocandins preferred.<br>Suspect *Candida* vegetations when lesions are large on echocardiography. |
| **Endocarditis Prophylaxis**[181,183,184]: Given that (1) endocarditis is rarely caused by dental/GI procedures and (2) prophylaxis for procedures prevents an exceedingly small number of cases, the risks of antibiotics outweigh the benefits. Highest risk conditions currently recommended for prophylaxis: (1) prosthetic heart valve (or prosthetic material used to repair a valve); (2) previous endocarditis; (3) cyanotic congenital heart disease that is unrepaired (or palliatively repaired with shunts and conduits); (4) congenital heart disease that is repaired but with defects at the site of repair adjacent to prosthetic material; (5) completely repaired congenital heart disease using prosthetic material, for the first 6 mo after repair; or (6) cardiac transplant patients with valvulopathy. Routine prophylaxis no longer is required for children with native valve abnormalities. Assessment of new prophylaxis guidelines documents no significant increase in endocarditis at this time.[181] | | |
| – In highest risk patients: dental procedures that involve manipulation of the gingival or periodontal region of teeth | Amoxicillin 50 mg/kg PO 60 min before procedure OR ampicillin or ceftriaxone or cefazolin, all at 50 mg/kg IM/IV 30–60 min before procedure | If penicillin allergy: clindamycin 20 mg/kg PO (60 min before) or IV (30 min before); OR azithromycin 15 mg/kg or clarithromycin 15 mg/kg, 60 min before |

| | | |
|---|---|---|
| – Genitourinary and GI procedures | None | No longer recommended |
| **Lemierre syndrome** (*Fusobacterium necrophorum* primarily, new reports with MRSA)[99,100,185,186] postanginal sepsis, pharyngitis with internal jugular vein septic thrombosis | Empiric: meropenem 60 mg/kg/day div q8h (or 120 mg/kg/day div q8h for CNS metastatic foci) (AIII) OR ceftriaxone 100 mg/kg/day q24h AND metronidazole 40 mg/kg/day div q8h or clindamycin 40 mg/kg/day div q6h (BIII).<br>ADD empiric vancomycin if MRSA suspected. | Anecdotal reports suggest metronidazole may be effective for apparent failures with other agents.<br>Metastatic and recurrent abscesses often develop while on active, appropriate therapy, requiring multiple debridements and prolonged antibiotic therapy. |
| **Purulent pericarditis** | | |
| – Empiric (acute, bacterial: *S aureus* [including MRSA], group A streptococcus, pneumococcus, meningococcus, *H influenzae* type b)[187,188] | Vancomycin 40 mg/kg/day IV div q8h AND ceftriaxone 50–75 mg/kg/day q24h (AIII).<br>For presumed staphylococcal infection, ADD gentamicin (AIII). | Increasingly uncommon with immunization against pneumococcus and *H influenzae* type b.[188] Pericardiocentesis is essential to establish diagnosis. Surgical drainage of pus with pericardial window or pericardiectomy is important to prevent tamponade. |
| – *S aureus* | For MSSA: oxacillin/nafcillin 150–200 mg/kg/day IV div q6h OR cefazolin 100 mg/kg/day IV div q8h. Treat for 2–3 wk after drainage (BIII).<br>For CA-MRSA: continue vancomycin. Treat for 3–4 wk after drainage (BIII). | Continue therapy with gentamicin; consider use of rifampin in severe cases. |
| – *H influenzae* type b in unimmunized children | Ceftriaxone 50 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h; for 10–14 days (AIII) | Ampicillin for beta-lactamase–negative strains |
| – Pneumococcus, meningococcus, group A streptococcus | Penicillin G 200,000 U/kg/day IV, IM div q6h for 10–14 days OR ceftriaxone 50 mg/kg qd for 10–14 days (AIII) | Ceftriaxone or cefotaxime for penicillin non-susceptible pneumococci |

## G. CARDIOVASCULAR INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – Coliform bacilli | Ceftriaxone 50–75 mg/kg/day q24h or cefotaxime 150 mg/kg/day div q8h for 3 wk or longer (AIII) | Alternative drugs depending on susceptibilities; for *Enterobacter, Serratia,* or *Citrobacter,* use cefepime or meropenem. For ESBL *E coli* or *Klebsiella*, use a carbapenem. |
| – Tuberculous[13,14] | INH 10–15 mg/kg/day (max 300 mg) PO, IV qd, for 6 mo AND rifampin 10–20 mg/kg/day (max 600 mg) PO qd, IV for 6 mo. ADD PZA 20–40 mg/kg/day PO qd for first 2 mo therapy; if suspected multidrug resistance, also add ethambutol 20 mg/kg/day PO qd (AIII). | Corticosteroids improve survival in adults. For children: prednisone 2 mg/kg/day for 4 wk, then 0.5 mg/kg/day for 4 wk, then 0.25 mg/kg/day for 2 wk, then 0.1 mg/kg/day for 1 wk (AIII).[13,14] |

## H. GASTROINTESTINAL INFECTIONS (See Chapter 10 for parasitic infections.)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Diarrhea/Gastroenteritis** | | |
| **Note on *E coli* and diarrheal disease:** Antibiotic susceptibility of *E coli* varies considerably from region to region. For mild to moderate disease, TMP/SMX may be started as initial therapy, but for more severe disease and for locations with rates of TMP/SMX resistance greater than 10% to 20%, oral 3rd-generation cephalosporins (eg, cefixime, cefdinir, ceftibuten), azithromycin, or ciprofloxacin should be used (AIII). Cultures and antibiotic susceptibility testing are recommended for significant disease (AIII). | | |
| – Empiric therapy of community-associated diarrhea in the United States (*E coli* [STEC, including O157:H7 strains, and ETEC], *Salmonella, Campylobacter,* and *Shigella* predominate; *Yersinia* and parasites causing <5%; however, viral pathogens are far more common, especially for children <3 y.)[189,190] | Azithromycin 10 mg/kg qd for 3 days (BII), OR cefixime 8 mg/kg/day PO qd (BII) for 5 days; OR ciprofloxacin 30 mg/kg/day PO div bid for 3 days | Alternatives: other oral 3rd-generation cephalosporins (eg, cefdinir, ceftibuten); or rifaximin 600 mg/day div tid for 3 days (for nonfebrile, non-bloody diarrhea for children >11 y).<br>Controversy exists regarding treatment of O157:H7 strains and the prevention or increased incidence of HUS, with retrospective data to support either treatment, or withholding treatment. Some experts treat with antimicrobials and others prefer to use supportive care.[191–194] |
| – Traveler's diarrhea: empiric therapy (*E coli, Campylobacter, Salmonella, Shigella,* plus many other pathogens, including protozoa)[195–201] | Azithromycin 10 mg/kg qd for 3 days (AII); OR rifaximin 600 mg/day div tid for 3 days (for nonfebrile, non-bloody diarrhea for children 12 y) (BII); OR cefixime 8–10 mg/kg qd for 5 days (CII); OR ciprofloxacin 30 mg/kg/day div bid for 3 days (CII) | Susceptibility patterns of *E coli, Campylobacter, Salmonella,* and *Shigella* vary widely by country; check country-specific data for departing or returning travelers. Azithromycin preferable to ciprofloxacin for travelers to Southeast Asia given high prevalence of quinolone-resistant *Campylobacter.*<br>Rifaximin is less effective than ciprofloxacin *for invasive bloody bacterial enteritis*; rifaximin may also not be as effective for *Shigella*, *Salmonella,* and *Campylobacter* as other agents.<br>Adjunctive therapy with loperamide (anti-motility) is not recommended for children <2 y and should be used only in nonfebrile, non-bloody diarrhea.[202,203] May shorten symptomatic illness by about 24 h. |

## H. GASTROINTESTINAL INFECTIONS (continued) (See Chapter 10 for parasitic infections.)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – Traveler's diarrhea: prophylaxis[195,196] | – Prophylaxis: Early self-treatment with agents listed previously is preferred over long-term prophylaxis, but may use prophylaxis for a short-term (<14 days) visit to very high-risk region: rifaximin (for older children), azithromycin, or bismuth subsalicylate (BIII). | |
| – *Aeromonas hydrophila*[204] | Ciprofloxacin 30 mg/kg/day PO div bid for 5 days OR azithromycin 10 mg/kg qd for 3 days OR cefixime 8 mg/kg/day PO qd (BIII) | Not all strains produce enterotoxins and diarrhea; role in diarrhea questioned.[204] Resistance to TMP/SMX about 10%–15%. Choose most narrow spectrum agent based on in vitro susceptibilities. |
| – *Campylobacter jejuni*[205–207] | Azithromycin 10 mg/kg/day for 3 days (BII) or erythromycin 40 mg/kg/day PO div qid for 5 days (BII) | Alternatives: doxycycline or ciprofloxacin (high rate of fluoroquinolone resistance in Thailand, India, and now the US).<br>Single-dose azithromycin (1 g, once) is effective in adults. |
| – Cholera[200,208] | Azithromycin 20 mg/kg once; OR erythromycin 50 mg/kg/day PO div qid for 3 days; OR doxycycline 4 mg/kg/day (max 200 mg/day) PO div bid, for all ages | Ciprofloxacin or TMP/SMX (if susceptible) |
| – *Clostridium difficile* (antibiotic-associated colitis)[209,210–212] | Metronidazole 30 mg/kg/day PO div qid OR vancomycin 40 mg/kg/day PO div qid for 7 days; for relapsing *C difficile* enteritis, consider pulse therapy (1 wk on/1 wk off for 3–4 cycles) or prolonged tapering therapy.[209] | Vancomycin is more effective for severe infection.[211]<br>Fidaxomicin approved for adults; pediatric studies underway.<br>Many infants and children may have asymptomatic colonization with *C difficile*.[211]<br>Higher risk of relapse in children with multiple comorbidities. |
| – *E coli* | | |
| Enterotoxigenic (etiology of most traveler's diarrhea)[197,199] | Azithromycin 10 mg/kg qd for 3 days; OR cefixime 8 mg/kg/day PO qd for 3 days; OR ciprofloxacin 30 mg/kg/day PO div bid for 3 days | Most illnesses brief and self-limited.<br>Alternatives: rifaximin 600 mg/day div tid for 3 days (for nonfebrile, non-bloody diarrhea for children >11 y); OR TMP/SMX.<br>Resistance increasing worldwide; check country-specific rates, if possible.[199] |

| | | |
|---|---|---|
| Enterohemorrhagic (O157:H7; STEC, etiology of HUS)[191–193] | Controversy on whether treatment of O157:H7 diarrhea results in more or less toxin-mediated renal damage.[191–193] For severe infection, treat as for enterotoxigenic strains above. | Injury to colonic mucosa may lead to invasive bacterial colitis. |
| Enteropathogenic | Neomycin 100 mg/kg/day PO div q6–8h for 5 days | Most traditional "enteropathogenic" strains are not toxigenic or invasive. Postinfection diarrhea may be problematic. |
| – Gastritis, peptic ulcer disease (*Helicobacter pylori*)[213–216] | Triple agent therapy: clarithromycin 7.5 mg/kg/dose 2–3 times each day, AND amoxicillin 40 mg/kg/dose (max 1 g) PO bid AND omeprazole 0.5 mg/kg/dose PO bid 10-14 days (BII).<br>Sequential therapy using 5 days of amox and omeprazole followed by 5 days of clarithromycin, metronidazole, and omeprazole is effective for susceptible strains.[215] | Most data from studies in adults; of effective regimens, no one combination has been shown superior. New, current regimens use 4 drugs (with metronidazole) initially or with relapse due to concerns for clarithromycin resistance.[213,215] Other regimens include bismuth, metronidazole instead of amoxicillin, and other proton pump inhibitors. |
| – Giardiasis (*Giardia intestinalis,* formerly *lamblia*)[217] | Metronidazole 30–40 mg/kg/day PO div tid for 7–10 days (BII); OR nitazoxanide PO (take with food), age 12–47 mo, 100 mg/dose bid for 7 days; age 4–11 y, 200 mg/dose bid for 7 days; age ≥12 y, 1 tab (500 mg)/dose bid for 7 days (BII); OR tinidazole 50 mg/kg/day (max 2 g) for 1 day (BII) | If therapy is inadequate, another course of the same agent is usually curative.<br>Alternatives: furazolidone 6 mg/kg/day in 4 doses for 7–10 days; OR paromomycin 30 mg/kg/day div tid for 5–10 days; OR albendazole 10 mg/kg/day PO for 5 days (CII).<br>Prolonged courses may be needed for immunocompromised conditions (eg, hypogammaglobulinemia).<br>Treatment of asymptomatic carriers not usually recommended. |

**H. GASTROINTESTINAL INFECTIONS** (continued) (See Chapter 10 for parasitic infections.)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – Salmonellosis | | |
| Non-typhoid strains[218] | Usually none for self-limited diarrhea in immunocompetent child (eg, diarrhea is much improved by the time culture results are available)<br>For persisting symptomatic infection: azithromycin 10 mg/kg PO qd for 3 days (AII); OR ceftriaxone 75 mg/kg/day IV, IM q24h for 5 days (AII); OR cefixime 20–30 mg/kg/day PO for 5 days (BII); OR for susceptible strains: TMP/SMX 8 mg/kg/day of TMP PO div bid for 5 days (AI) | Alternatives: ciprofloxacin 30 mg/kg/day PO div bid for 5 days (AI).<br>Carriage of strains may be prolonged in treated children. |
| Typhoid fever[219–222] | Azithromycin 10 mg/kg qd for 5 days (AII); OR ceftriaxone 75 mg/kg/day IV, IM q24h for 5 days (AII); OR cefixime 20–30 mg/kg/day PO, div q12h for 14 days (BII); OR for susceptible strains: TMP/SMX 8 mg/kg/day of TMP PO div bid for 10 days (AI) | Increasing cephalosporin resistance. Watch for relapse if ceftriaxone used.<br>Longer treatment courses for focal metastatic invasive disease (eg, osteomyelitis).<br>Alternative: ciprofloxacin 30 mg/kg/day PO div bid for 5–7 days (AI). |
| – Shigellosis[223–225] | Cefixime 8 mg/kg/day PO qd for 5 days (AII); OR azithromycin 10 mg/kg/day PO for 3 days (AII); OR ciprofloxacin 30 mg/kg/day PO div bid for 3–5 days (BII) | Alternatives for susceptible strains: TMP/SMX 8 mg/kg/day of TMP PO div bid for 5 days; OR ampicillin (*not* amoxicillin).<br>Ceftriaxone 50 mg/kg/day IM, IV if parenteral therapy necessary, for 2–5 days.<br>Avoid antiperistaltic drugs.<br>Treatment for the improving child is not usually necessary, but some experts would treat to decrease communicability. |
| – *Yersinia enterocolitica*[226,227] | Antimicrobial therapy probably not of value for mild disease in normal hosts<br>TMP/SMX PO, IV; OR ciprofloxacin PO, IV (BIII) | Alternatives: ceftriaxone or gentamicin.<br>High rates of resistance to ampicillin.<br>May mimic appendicitis in older children.<br>Limited clinical data exist on oral therapy. |

| Intra-abdominal Infection (abscess, peritonitis secondary to bowel/appendix contents) | | |
|---|---|---|
| – Appendicitis; bowel-associated (enteric gram-negative bacilli, *Bacteroides* spp, *Enterococcus* spp, increasingly *Pseudomonas*)[228–233] | Meropenem 60 mg/kg/day IV div q8h or imipenem 60 mg/kg/day IV div q6h; OR pip/tazo 240 mg pip/kg/day div q6h; for 4–5 days for patients with adequate source control,[232] 7–10 days or longer if suspicion of persisting intra-abdominal abscess (AII).<br>Data support IV outpatient therapy or oral step-down therapy[233] when clinically improved. | Many other regimens may be effective, including ampicillin 150 mg/kg/day div q8h AND gentamicin 6–7.5 mg/kg/day IV, IM div q8h AND metronidazole 40 mg/kg/day IV div q8h; OR ceftriaxone 50 mg/kg q24h AND metronidazole 40 mg/kg/day IV div q8h.<br>Gentamicin demonstrates poor activity at low pH: surgical source control is critical to achieve cure. |
| – Tuberculosis, abdominal (*Mycobacterium bovis,* from unpasteurized dairy products)[13,14,234,235] | INH 10–15 mg/kg/day (max 300 mg) PO qd for 6 mo AND rifampin 10–20 mg/kg/day (max 600 mg) PO qd for 6 mo.<br>*M bovis* is resistant to PZA.<br>If risk factors are present for multidrug resistance (eg, poor adherence to previous therapy), add ethambutol 20 mg/kg/day PO qd OR a fluoroquinolone (moxifloxacin or levofloxacin). | Directly observed therapy preferred; after 2+ wk of daily therapy, can change to twice-weekly dosing double dosage of INH (max 900 mg); rifampin remains same dosage (10–20 mg/kg/day, max 600 mg) (AII).<br>LP ± CT of head for children ≤2 y with active disease to rule out occult, concurrent CNS infection (AIII). |
| **Perirectal abscess** (*Bacteroides* spp, other anaerobes, enteric bacilli, and *S aureus* predominate)[236] | Clindamycin 30–40 mg/kg/day IV div q8h AND cefotaxime or ceftriaxone or gentamicin (BIII) | Surgical drainage alone may be curative. |

**H. GASTROINTESTINAL INFECTIONS** (continued) (See Chapter 10 for parasitic infections.)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Peritonitis**<br>– Peritoneal dialysis indwelling catheter infection (staphylococcal; enteric gram-negatives; yeast)[237,238] | Antibiotic added to dialysate in concentrations approximating those attained in serum for systemic disease (eg, 4 µg/mL for gentamicin, 25 µg/mL for vancomycin, 125 µg/mL for cefazolin, 25 µg/mL for ciprofloxacin) after a larger loading dose (AII)[238] | Selection of antibiotic based on organism isolated from peritoneal fluid; systemic antibiotics if there is accompanying bacteremia/fungemia |
| – Primary (pneumococcus or group A streptococcus)[239] | Ceftriaxone 50 mg/kg/day q24h, or cefotaxime 150 mg/kg/day div q8h; if pen-S, then penicillin G 150,000 U/kg/day IV div q6h; for 7–10 days (AII) | Other antibiotics according to culture and susceptibility tests |

## I. GENITAL AND SEXUALLY TRANSMITTED INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| Consider testing for HIV and other STIs in a child with one documented STI; consider sexual abuse in prepubertal children. The most recent CDC STI treatment guidelines are posted online at www.cdc.gov/std/treatment. | | |
| **Chancroid** (*Haemophilus ducreyi*)[42] | Azithromycin 1 g PO as single dose OR ceftriaxone 250 mg IM as single dose | Alternative: erythromycin 1.5 g/day PO div tid for 7 days OR ciprofloxacin 1,000 mg PO qd, div bid for 3 days |
| ***C trachomatis*** (cervicitis, urethritis)[42,240] | Azithromycin 20 mg/kg (max 1 g) PO for 1 dose; OR doxycycline (patients >7 y) 4 mg/kg/day (max 200 mg/day) PO div bid for 7 days | Alternatives: erythromycin 2 g/day PO div qid for 7 days; OR levofloxacin 500 mg PO q24h for 7 days |
| **Epididymitis** (associated with positive urine cultures and STIs)[42,241,242] | Ceftriaxone 50 mg/kg/day q24h for 7–10 days AND (for older children) doxycycline 200 mg/day div bid for 10 days | Microbiology not well studied in children; in infants, also associated with urogenital tract anomalies.<br>Treat infants for *S aureus* and *E coli;* may resolve spontaneously; in STI, caused by *Chlamydia* and gonococcus. |
| **Gonorrhea** | | |
| – Newborns | See Chapter 5. | |
| – Genital infections (uncomplicated vulvovaginitis, cervicitis, urethritis, or proctitis)[42,240,243,244] | Ceftriaxone 250 mg IM for 1 dose (regardless of weight) AND azithromycin 1 g PO for 1 dose or doxycycline 200 mg/day div q12h for 7 days | Cefixime no longer recommended due to increasing cephalosporin resistance.[244]<br>Fluoroquinolones are no longer recommended due to resistance.[245] |
| – Pharyngitis[42,244,245] | Ceftriaxone 250 mg IM for 1 dose (regardless of weight) AND azithromycin 1 g PO for 1 dose or doxycycline 200 mg/day div q12h for 7 days | |
| – Conjuctivitis[42] | Ceftriaxone 1g IM for 1 dose AND azithromycin 1 g PO for 1 dose | Lavage the eye with saline. |
| – Disseminated gonococcal infection[42,244,245] | Ceftriaxone 50 mg/kg/day IM, IV q24h (max: 1 g) AND azithromycin 1 g PO for 1 dose; total course for 7 days | No studies in children: increase dosage for meningitis. |

## I. GENITAL AND SEXUALLY TRANSMITTED INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Granuloma inguinale** (donovanosis, *Klebsiella granulomatis,* formerly *Calymmatobacterium*)[42] | Azithromycin 1 g orally once per week or 500 mg daily for at least 3 weeks and until all lesions have completely healed | Primarily in tropical regions of India, Pacific, and Africa.<br>Options: Doxycycline 4 mg/kg/day div bid (max 200 mg/day), PO for at least 3 weeks OR ciprofloxacin 750 mg PO bid for at least 3 weeks, OR erythromycin base 500 mg PO 4 times a day for at least 3 wk OR TMP/SMX 1 double-strength (160 mg/800 mg) tablet PO bid for at least 3 wk; all regimens continue until all lesions have completely healed. |
| **Herpes simplex virus, genital infection**[42,246,247] | Acyclovir 20 mg/kg/dose (max 400 mg) PO tid for 7–10 days (first episode) (AI); OR valacyclovir 20 mg/kg/dose of extemporaneous suspension (directions on package label), max 1.0 g PO bid for 7–10 days (first episode) (AI); OR famciclovir 250 mg PO tid for 7–10 days (AI); for more severe infection: acyclovir 15 mg/kg/day IV div q8h as 1-h infusion for 7–10 days (AII) | For recurrent episodes: treat with acyclovir PO, valacyclovir PO, or famciclovir PO, immediately when symptoms begin, for 5 days.<br>For suppression: acyclovir 20 mg/kg/dose (max 400 mg) PO bid; OR valacyclovir 20 mg/kg/dose PO qd (little long-term safety data in children; no efficacy data in children). |
| **Lymphogranuloma venereum** (*C trachomatis*)[42] | Doxycycline 4 mg/kg/day (max 200 mg/day) PO (patients >7 y) div bid for 21 days | Alternatives: erythromycin 2 g/day PO div qid for 21 days; OR azithromycin 1 g PO once weekly for 3 wk |
| **Pelvic inflammatory disease** (*Chlamydia,* gonococcus, plus anaerobes)[42,248] | Cefoxitin 2 g IV q6h; AND doxycycline 200 mg/day PO or IV div bid; OR cefotetan 2 g IV q12h AND doxycycline 100 mg orally or IV q12h, OR clindamycin 900 mg IV q8h AND gentamicin 1.5 mg/kg IV, IM q8h for 14 days | Drugs given IV until clinical improvement for 24 h, followed by doxycycline 200 mg/day PO div bid AND clindamycin 1,800 mg/day PO div qid to complete 14 days of therapy<br>Optional regimen: ceftriaxone 250 mg IM for 1 dose AND doxycycline 200 mg/day PO div bid; WITH/WITHOUT metronidazole 1 g/day PO div bid; for 14 days |
| **Syphilis**[42,249] (test for HIV) | | |

| | | |
|---|---|---|
| – Congenital | See Chapter 5. | |
| – Neurosyphilis (positive CSF VDRL or CSF pleocytosis with serologic diagnosis of syphilis) | Crystalline penicillin G 200–300,000 U/kg/day (max 24,000,000 U/day) div q6h for 10–14 days (AIII) | |
| – Primary, secondary | Benzathine penicillin G 50,000 U/kg (max 2,400,000 U) IM as a single dose (AIII); do not use benzathine-procaine penicillin mixtures. | Follow-up serologic tests at 6, 12, and 24 mo; 15% may remain seropositive despite adequate treatment. If allergy to penicillin: doxycycline (patients >7 y) 4 mg/kg/day (max 200 mg) PO div bid for 14 days.<br>CSF examination should be obtained for children being treated for primary or secondary syphilis to rule out asymptomatic neurosyphilis.<br>Test for HIV. |
| – Syphilis of <1 y duration, without clinical symptoms (early latent syphilis) | Benzathine penicillin G 50,000 U/kg (max 2,400,000 U) IM as a single dose (AIII) | Alternative if allergy to penicillin: doxycycline (patients >7 y) 4 mg/kg/day (max 200 mg/day) PO div bid for 14 days |
| – Syphilis of >1 y duration, without clinical symptoms (late latent syphilis) or syphilis of unknown duration | Benzathine penicillin G 50,000 U/kg (max 2,400,000 U) IM weekly for 3 doses (AIII) | Alternative if allergy to penicillin: doxycycline (patients >7 y) 4 mg/kg/day (max 200 mg/day) PO div bid for 28 days.<br>Look for neurologic, eye, and aortic complications of tertiary syphilis. |
| **Trichomoniasis**[42] | Metronidazole 2 g PO as a single dose, OR tinidazole 50 mg/kg (max 2 g) PO for 1 dose | Metronidazole 500 mg PO bid for 7 days |
| **Urethritis, nongonococcal** (See "Gonorrhea" for gonorrhea therapy.)[42] | Azithromycin 20 mg/kg (max 1 g) PO for 1 dose, OR doxycycline (patients >7 y) 40 mg/kg/day (max 200 mg/day) PO div bid for 7 days (AII) | Erythromycin, levofloxacin, or ofloxacin |

## I. GENITAL AND SEXUALLY TRANSMITTED INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Vaginitis**[42] | | |
| – Bacterial vaginosis[250] | Metronidazole 500 mg PO twice daily for 7 days OR metronidazole vaginal gel (0.75%) qd for 5 days, OR clindamycin vaginal cream for 7 days | Alternative: tinidazole 1 g PO qd for 5 days, OR clindamycin 300 mg PO bid for 7 days<br>Relapse common<br>Caused by synergy of *Gardnerella* with anaerobes |
| – Candidiasis, vulvovaginal[42,251] | Fluconazole 5 mg/kg PO (max 150 mg) for 1 dose; topical treatment with azole creams (see Comments). | Many topical vaginal azole agents are available without prescription (eg, butoconazole, clotrimazole, miconazole, tioconazole) and some require a prescription for unique agents or unique dosing regimens (terconazole, butoconazole). |
| – Prepubertal vaginitis[252] | No prospective studies | Cultures from symptomatic prepubertal girls are statistically more likely to yield *E coli*, enterococcus, coagulase-negative staphylococci, and streptococci (viridans strep and group A strep), but these organisms may also be present in asymptomatic girls. |
| – *Shigella*[253] | Cefixime 8 mg/kg/day PO qd for 5 days OR ciprofloxacin 30 mg/kg/day PO div bid for 5 days | 50% have bloody discharge; usually not associated with diarrhea. |
| – *Streptococcus*, group A[254] | Penicillin V 50–75 mg/kg/day PO div tid for 10 days | Amoxicillin 50–75 mg/kg/day PO div tid |

## J. CENTRAL NERVOUS SYSTEM INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Abscess, brain** (respiratory tract flora, skin flora, or bowel flora, depending on the pathogenesis of infection based on underlying comorbid disease and origin of bacteremia)[255,256] | Until etiology established, cover flora of respiratory tract, skin, and/or bowel, based on individual patient evaluation: meropenem 120 mg/kg/day div q8h (AIII); OR nafcillin 150–200 mg/kg/day IV div q6h AND cefotaxime 200–300 mg/kg/day IV div q6h or ceftriaxone 100 mg/kg/day IV q24h AND metronidazole 30 mg/kg/day IV div q8h (BIII); for 2–3 wk after successful drainage (depending on pathogen, size of abscess, and response to therapy); longer course if no surgery (3–6 wk) (BIII). | Surgery for abscesses ≥2 cm diameter.<br>If CA-MRSA suspected, ADD vancomycin 60 mg/kg/day IV div q8h ± rifampin 20 mg/kg/day IV div q12h, pending culture results.<br>If secondary to chronic otitis, include meropenem or cefepime in regimen for anti-*Pseudomonas* activity.<br>For enteric gram-negative bacilli, consider ESBL-producing *E coli* and *Klebsiella* that require meropenem and are resistant to cefotaxime.<br>Follow abscess size by CT. |
| **Encephalitis**[257,258] | | |
| – Amebic (*Naegleria fowleri*, *Balamuthia mandrillaris*, and *Acanthamoeba*) | See Chapter 10, Amebiasis. | |
| – CMV[257] | Not studied in children. Consider ganciclovir 10 mg/kg/day IV div q12h; for severe immunocompromised, ADD foscarnet 180 mg/kg/day IV div q8h for 3 wk; follow quantitative PCR for CMV. | High-dose ganciclovir[259] (IV 20 mg/kg/day div q12h) not well studied. Reduce dose for renal insufficiency. Watch for neutropenia. |
| – Enterovirus | Supportive therapy; no antivirals currently FDA approved | Pocapavir PO is currently under investigation for enterovirus (poliovirus). |
| – EBV[260] | Not studied in a controlled comparative trial. Consider ganciclovir 10 mg/kg/day IV div q12h or acyclovir 60 mg/kg/day IV div q8h for 3 wk; follow quantitative PCR in CSF for EBV. | Efficacy of antiviral therapy not well defined; some experts recommend against antiviral treatment.[257] |

## J. CENTRAL NERVOUS SYSTEM INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – Herpes simplex virus[257,261] | Acyclovir 60 mg/kg/day IV as 1–2 h infusion div q8h; for 21 days for infants ≤4 mo. For older infants and children, 45–60 mg/kg/day IV for 21 days (AIII). | See Chapter 5 for neonatal infection.<br>Safety of high-dose acyclovir (60 mg/kg/day) not well defined beyond the neonatal period; can be used, but monitor for neurotoxicity and nephrotoxicity; FDA has approved acyclovir at this dosage for encephalitis for children up to 12 y. |
| – *Toxoplasma* | See Chapter 10. | |
| – Arbovirus (flavivirus—West Nile, St Louis encephalitis, tick-borne encephalitis; togavirus—Western equine encephalitis, Eastern equine encephalitis; bunyavirus—La Crosse encephalitis, California encephalitis)[257,258] | Supportive therapy | Investigational only (antiviral, interferon, immune globulins) |
| **Meningitis, bacterial, community-associated** | | |
| **NOTES**<br>– In areas where pen-R pneumococci exist (>5% of invasive strains), initial empiric therapy for suspect pneumococcal meningitis should be with vancomycin AND cefotaxime or ceftriaxone until susceptibility test results are available.<br>– Dexamethasone 0.6 mg/kg/day IV div q6h for 2 days as an adjunct to antibiotic therapy decreases hearing deficits and other neurologic sequelae in adults and children (for *Haemophilus* and pneumococcus; not prospectively studied in children for meningococcus or *E coli*). The first dose of dexamethasone is given before or concurrent with the first dose of antibiotic; probably little benefit if given ≥1 h after the antibiotic.[262,263]<br>– We hope to see more data on osmotic therapy before we recommend it, as early data suggesting benefits of oral glycerol have not been substantiated to date.[264,265] | | |
| – Empiric therapy[266] | Cefotaxime 200–300 mg/kg/day IV div q6h, or ceftriaxone 100 mg/kg/day IV q24h; AND vancomycin 60 mg/kg/day IV div q8h (AII) | If Gram stain or cultures demonstrate a pathogen other than pneumococcus, vancomycin is not needed; vancomycin used empirically only for possible pen-R pneumococcus. |

| | | |
|---|---|---|
| – *H influenzae* type b[266] | Cefotaxime 200–300 mg/kg/day IV div q6h, or ceftriaxone 100 mg/kg/day IV q24h; for 10 days (AI) | Alternative: ampicillin 200–400 mg/kg/day IV div q6h (for beta-lactamase–negative strains) OR chloramphenicol 100 mg/kg/day IV div q6h |
| – Meningococcus (*Neisseria meningitidis*)[266] | Penicillin G 250,000 U/kg/day IV div q4h; or ceftriaxone 100 mg/kg/day IV q24h, or cefotaxime 200 mg/kg/day IV div q6h; treatment course for 7 days (AI) | Meningococcal prophylaxis: rifampin 10 mg/kg PO q12h for 4 doses OR ceftriaxone 125–250 mg IM once OR ciprofloxacin 500 mg PO once (adolescents and adults) |
| – Neonatal | See Chapter 5. | |
| – Pneumococcus (*S pneumoniae*)[266] | For pen-S and cephalosporin-susceptible strains: penicillin G 250,000 U/kg/day IV div q4–6h, OR ceftriaxone 100 mg/kg/day IV q24h or cefotaxime 200–300 mg/kg/day IV div q6h; for 10 days (AI).<br>For pen-R pneumococci: continue the combination of vancomycin and cephalosporin IV for total course (AIII). | Some pneumococci may be resistant to penicillin but susceptible to cefotaxime and ceftriaxone and may be treated with the cephalosporin alone.<br>With the efficacy of current pneumococcal conjugate vaccines, primary bacterial meningitis is uncommon, and penicillin resistance has decreased substantially.<br>Test-of-cure LP helpful in those with pen-R pneumococci. |
| **Meningitis, TB** (*M tuberculosis; M bovis*)[13,14] | For non-immunocompromised children: INH 15 mg/kg/day PO, IV div q12–24h AND rifampin 15 mg/kg/day PO, IV, div q12–24h for 12 mo AND PZA 30 mg/kg/day PO div q12–24h for first 2 mo of therapy, AND streptomycin 30 mg/kg/day IV, IM div q12h for first 4–8 wk of therapy until susceptibility test results available. Ethionamide is an alternative to aminoglycosides. | Hyponatremia from inappropriate ADH secretion is common; ventricular drainage may be necessary for obstructive hydrocephalus.<br>Corticosteroids (can use the same dexamethasone dose as for bacterial meningitis, 0.6 mg/kg/day IV div q6h) for 4 wk until neurologically stable, then taper dose for 1–3 mo to decrease neurologic complications and improve prognosis by decreasing the incidence of infarction.[267] Watch for rebound inflammation during taper; increase dose to previously effective level, then taper more slowly.<br>For recommendations for drug-resistant strains and treatment of TB in HIV-infected patients, visit the CDC Web site for TB: www.cdc.gov/tb (accessed August 28, 2015). |

## J. CENTRAL NERVOUS SYSTEM INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Shunt infections:** The use of antibiotic-impregnated shunts has decreased the frequency of this infection.[268] Shunt removal is usually necessary for cure.[269] | | |
| – Empiric therapy pending Gram stain and culture[266,269] | Vancomycin 60 mg/kg/day IV div q8h, AND ceftriaxone 100 mg/kg/day IV q24h (AII) | If Gram stain shows only gram-positive cocci, can use vancomycin alone.<br>Cefepime or meropenem should be used instead of ceftriaxone if *Pseudomonas* is suspected. |
| – *S epidermidis* or *S aureus*[266,269] | Vancomycin (for *S epidermidis* and CA-MRSA) 60 mg/kg/day IV div q8h; OR nafcillin (if organisms susceptible) 150–200 mg/kg/day AND (if severe infection or slow response) gentamicin or rifampin; for 10–14 days (AIII) | Shunt removal usually necessary; may need to treat with ventriculostomy until ventricular CSF cultures negative; obtain CSF cultures at time of shunt replacement, continue therapy an additional 48–72 h pending cultures.<br>For children who cannot tolerate vancomycin, ceftaroline has anecdotally been successful. |
| – Gram-negative bacilli[266,269] | Empiric therapy with meropenem 120 mg/kg/day IV div q8h OR cefepime 150 mg/kg/day IV div q8h (AIII)<br>For *E coli:* ceftriaxone 100 mg/kg/day IV q12h OR cefotaxime 200–300 mg/kg/day IV div q6h; ADD gentamicin 6–7.5 mg/kg/day IV until CSF sterile; for 21 days or longer | Remove shunt. Select appropriate therapy based on in vitro susceptibilities.<br>Intrathecal therapy with aminoglycosides not routinely necessary with highly active beta-lactam therapy and shunt removal. |

## K. URINARY TRACT INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **NOTE:** Antibiotic susceptibility profiles of *E coli,* the most common cause of UTI, vary considerably. For mild disease, TMP/SMX may be started as initial therapy if local susceptibility ≥80% and a 20% failure rate is acceptable. For moderate to severe disease (possible pyelonephritis), obtain cultures and begin oral 2nd- or 3rd-generation cephalosporins (cefuroxime, cefaclor, cefprozil, cefixime, ceftibuten, cefdinir, cefpodoxime), ciprofloxacin PO, or ceftriaxone IM. Antibiotic susceptibility testing will help direct your therapy to the most narrow spectrum agent. | | |
| **Cystitis, acute**<br>(*E coli*)[270,271] | For mild disease: TMP/SMX 8 mg/kg/day of TMP PO div bid for 3 days (See NOTE above about resistance to TMP/SMX.)<br>For moderate to severe disease: cefixime 8 mg/kg/day PO qd; OR ceftriaxone 50 mg/kg IM q24h for 3–5 days (with normal anatomy) (BII); follow-up culture after 36–48 h treatment ONLY if still symptomatic | Alternative: amoxicillin 30 mg/kg/day PO div tid if susceptible (BII); ciprofloxacin 15–20 mg/kg/day PO div bid for resistant organisms |
| **Nephronia, lobar**<br>*E coli* and other enteric rods (also called focal bacterial nephritis)[272] | Ceftriaxone 50 mg/kg/day IV, IM q24h.<br>Duration depends on resolution of cellulitis vs development of abscess (10–21 days) (AIII). | Invasive, consolidative parenchymal infection; complication of pyelonephritis, can evolve into renal abscess. Step down therapy with oral cephalosporins once cellulitis/abscess has initially responded to therapy. |
| **Pyelonephritis, acute**<br>(*E coli*)[270,271,273–276] | Ceftriaxone 50 mg/kg/day IV, IM q24h OR gentamicin 5–6 mg/kg/day IV, IM q24h.<br>For documented or suspected ceftriaxone-resistant ESBL-positive strains, use meropenem IV, imipenem IV, or ertapenem IV; OR gentamicin IV, IM, OR pip/tazo.<br>Switch to oral therapy following clinical response (BII). If organism resistant to amoxicillin and TMP/SMX, use an oral 2nd- or 3rd-generation cephalosporin (BII); if cephalosporin-R, can use ciprofloxacin PO 30 mg/kg/day div q12h (BIII); for 7–10 days total (depending on response to therapy). | For mild to moderate infection, oral therapy is likely to be as effective as IV/IM therapy for susceptible strains, down to 3 mo of age.[274]<br>If bacteremia documented and infant is <2–3 mo, rule out meningitis and treat 14 days IV + PO (AIII).<br>Aminoglycosides at any dose are more nephrotoxic than beta-lactams but represent effective therapy (AI). |

## K. URINARY TRACT INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Recurrent urinary tract infection, prophylaxis**[270,277–279] | Only for those with grade III–V reflux or with recurrent febrile UTI: TMP/SMX 2 mg/kg/dose of TMP PO qd OR nitrofurantoin 1–2 mg/kg PO qd at bedtime; more rapid resistance may develop using beta-lactams (BII). | Prophylaxis not recommended for patients with grade I–II reflux and no evidence of renal damage (although the RIVUR study included these children). Early treatment of new infections is recommended for these children.<br>*Resistance eventually develops to every antibiotic*; follow resistance patterns for each patient. |

## L. MISCELLANEOUS SYSTEMIC INFECTIONS

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Actinomycosis**[280,281] | Penicillin G 250,000 U/kg/day IV div q6h, or ampicillin 150 mg/kg/day IV div q8h until improved (often up to 6 wk); then long-term convalescent therapy with penicillin V 100 mg/kg/day (up to 4 g/day) PO for 6–12 mo (AII) | Surgery as indicated<br>Alternatives: amoxicillin, clindamycin, erythromycin; ceftriaxone IM/IV, doxycycline for children >7 y |
| **Anaplasmosis**[282] (human granulocytotropic anaplasmosis, *Anaplasma phagocytophilum*) | Doxycycline 4 mg/kg/day IV, PO (max 200 mg/day) div bid for 7–10 days (regardless of age) (AIII) | For mild disease, consider rifampin 20 mg/kg/day PO div bid for 7–10 days (BIII). |
| **Anthrax, sepsis/pneumonia, community vs bioterror exposure** (inhalation, cutaneous, gastrointestinal, meningoencephalitis)[15,283] | For community-associated anthrax infection, amoxicillin 75 mg/kg/day div q8h or doxycycline for children >7 y should be effective<br>For bioterror-associated exposure (regardless of age): ciprofloxacin 20–30 mg/kg/day IV div q12h, OR levofloxacin 16 mg/kg/day IV div q12h not to exceed 250 mg/dose (AIII); OR doxycycline 4 mg/kg/day PO (max 200 mg/day) div bid (regardless of age). | For invasive infection after bioterror exposure, 2 or 3 antibiotics may be required.[283]<br>For oral step-down therapy, can use oral ciprofloxacin or doxycycline; if susceptible, can use penicillin, amoxicillin, or clindamycin. |
| **Appendicitis** (See Peritonitis.) | | |
| **Brucellosis**[284–287] | Doxycycline 4 mg/kg/day PO (max 200 mg/day) div bid (for children >7 y) AND rifampin (15–20 mg/kg/day div q12h) (BIII); OR for children <8 y: TMP/SMX 10 mg/kg/day TMP IV, PO div q12h AND rifampin 15–20 mg/kg/day div q12h (BIII); for 4–8 wk | Combination therapy with rifampin will decrease the risk of relapse.<br>ADD gentamicin 6–7.5 mg/kg/day IV, IM div q8h for the first 1–2 wk of therapy to further decrease risk of relapse[286] (BIII), particularly for endocarditis, osteomyelitis, or meningitis.<br>Prolonged treatment for 4–6 mo and surgical debridement may be necessary for deep infections (AIII). |

## L. MISCELLANEOUS SYSTEMIC INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Cat-scratch disease** (*Bartonella henselae*)[288,289] | Supportive (I&D of infected lymph node); azithromycin 12 mg/kg/day PO qd for 5 days shortens the duration of adenopathy (AIII). | This dosage of azithromycin has been documented to be safe and effective for streptococcal pharyngitis and may offer greater deep tissue exposure than the dosage studied by Bass et al[8] and used for otitis media.<br>No prospective data exist for invasive infections: gentamicin (for 14 days) AND TMP/SMX AND rifampin for hepatosplenic disease and osteomyelitis (AIII). For CNS infection, use cefotaxime AND gentamicin ± TMP/SMX (AIII).<br>Alternatives: ciprofloxacin, doxycycline. |
| **Chickenpox/shingles** (varicella-zoster virus)[290,291] | Acyclovir 30 mg/kg/day IV as 1–2 h infusion div q8h; for 10 days (acyclovir doses of 45–60 mg/kg/day in 3 div doses IV should be used for disseminated or CNS infection). Dosing can also be provided as 1,500 mg/m$^2$/day IV div q8h. Duration in immunocompromised children: 7–14 days, based on clinical response (AI).<br>For treatment in normal immunocompetent children, acyclovir 80 mg/kg/day PO div qid, for 5 days (AI).<br>Valacyclovir pharmacokinetics have been assessed in an extemporaneously[291] compounded suspension of crushed tablets and simple syrup (60 mg/kg/day div tid) for children 3 mo to 12 y; instructions for preparation provided in package insert, and shelf life is 28 days. | See Chapter 9; therapy for 10 days in immunocompromised children.<br>Famciclovir can be provided as 25- and 100-mg sprinkles (from capsules).[292] See Chapter 9 for dosages by body weight. No treatment data in children (CIII). |
| **Ehrlichiosis** (human monocytic ehrlichiosis, caused by *Ehrlichia chaffeensis,* and *Ehrlichia ewingii*)[293–295] | Doxycycline 4 mg/kg/day IV, PO div bid (max 100 mg/dose) for 7–10 days (regardless of age) (AIII) | For mild disease, consider rifampin 20 mg/kg/day PO div bid (max 300 mg/dose) for 7–10 days (BIII). |

| | | |
|---|---|---|
| **Febrile neutropenic patient** (empiric therapy of invasive infection: *Pseudomonas,* enteric gram-negative bacilli, staphylococci, streptococci, yeast, fungi)[296,297] | Cefepime 150 mg/kg/day div q8h (AI); or meropenem 60 mg/kg/day div q8h (AII); OR pip/tazo (300-mg piperacillin component/kg/day div q8h for 9 mo; 240 mg/kg/day div q8h for 2–9 mo), OR ceftazidime 150 mg/kg/day IV div q8h AND tobramycin 6 mg/kg/day IV q8h (AII).<br>ADD vancomycin 40 mg/kg/day IV div q8h if MRSA or coagulation-negative staph suspected (eg, central catheter infection) (AIII).<br>ADD metronidazole to ceftazidime or cefepime if colitis or other deep anaerobic infection suspected (AIII). | Alternatives: other anti-*Pseudomonas* beta-lactams (imipenem) AND anti-staphylococcal antibiotics.<br>If no response in 2–3 days and no alternative etiology demonstrated, begin additional empiric therapy with antifungals (BII); dosages and formulations outlined in Chapter 8.<br>Increasingly resistant pathogens (ESBL *E coli* and *Klebsiella,* KPC) will require alternative empiric therapy if MDR organisms are colonizing or present on the child's hospital unit.<br>For low-risk patients with close follow-up, oral therapy with amox/clav and ciprofloxacin may be used. |
| **Human immunodeficiency virus infection** | See Chapter 9. | |
| **Infant botulism**[298] | Botulism immune globulin for infants (BabyBIG) 50 mg/kg IV for 1 dose (AI); BabyBIG can be obtained from the California Department of Public Health at www.infantbotulism.org, through your state health department. | www.infantbotulism.org provides information for physicians and parents. Web site organized by the California Department of Public Health (accessed August 28, 2015).<br>Aminoglycosides should be avoided because they potentiate the neuromuscular effect of botulinum toxin. |

## L. MISCELLANEOUS SYSTEMIC INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| **Kawasaki syndrome**[299–303] | No antibiotics; IVIG 2 g/kg as single dose (AI); may need to repeat dose in up to 15% of children for persisting fever that lasts 24 h after completion of the IVIG infusion (AII). For subsequent relapse, consult an infectious disease physician or pediatric cardiologist. | Aspirin 80–100 mg/kg/day div qid in acute, febrile phase; once afebrile for 24–48 h, initiate low-dosage (3–5 mg/kg/day) aspirin therapy for 6–8 wk (assuming echocardiogram is normal).<br>Role of corticosteroids,[300,301] infliximab,[302] and calcineurin inhibitors for IVIG-resistant Kawasaki syndrome under investigation but may improve outcome in severe cases. |
| **Leprosy**<br>(Hansen disease)[304] | Dapsone 1 mg/kg/day PO qd AND rifampin 10 mg/kg/day PO qd; ADD (for multibacillary disease) clofazimine 1 mg/kg/day PO qd; for 12 mo for paucibacillary disease; for 24 mo for multibacillary disease (AII) | Consult Health Resources and Services Administration National Hansen's Disease (Leprosy) Program at www.hrsa.gov/hansensdisease (accessed August 28, 2015) for advice about treatment and free antibiotics: 800/642-2477. |
| **Leptospirosis**[305,306] | Penicillin G 250,000 U/kg/day IV div q6h, or ceftriaxone 50 mg/kg/day IV, IM q24h; for 7 days (BII)<br>For mild disease, doxycycline (>7 y) 4 mg/kg/day (max 200 mg/day) PO div bid for 7–10 days and for those ≤7 y or intolerant of doxycycline, azithromycin 20 mg/kg on day 1, 10 mg/kg on days 2 and 3 (BII) | Alternative: amoxicillin for children ≤7 y of age with mild disease |
| **Lyme disease**<br>***(Borrelia burgdorferi)***[295,307,308] | Neurologic evaluation, including LP, if there is clinical suspicion of CNS involvement | |
| – Early localized disease | >7 y: doxycycline 4 mg/kg/day (max 200 mg/day) PO div bid for 14 days (AII)<br>≤7 y: amoxicillin 50 mg/kg/day (max 1.5 g/day) PO div tid for 14 days (AII) | Alternative: cefuroxime, 30 mg/kg/day (max 1,000 mg/day) PO, in 2 div doses (or 1 g/day) for 14 days |

| | | |
|---|---|---|
| – Arthritis (no CNS disease) | Oral therapy as outlined previously; for 28 days (AIII) | Persistent or recurrent joint swelling after treatment: repeat a 4-wk course of oral antibiotics or give ceftriaxone 50–75 mg/kg IV q24h OR penicillin 300,000 U/kg/day IV div q4h; either for 14–28 days.<br>For persisting arthritis after 2 defined antibiotic treatment courses, use symptomatic therapy. |
| – Erythema migrans | Oral therapy as outlined previously; for 14 days (AIII) | |
| – Isolated facial (Bell) palsy | Oral therapy as outlined previously; for 21–28 days (AIII) | LP is not routinely required unless CNS symptoms present. Treatment to prevent late sequelae; will not provide a quick response for palsy. |
| – Carditis | Ceftriaxone 50–75 mg/kg IV q24h OR penicillin 300,000 U/kg/day IV div q4h; for 14–21 days (AIII) | For asymptomatic disease, treat with oral regimen as for early localized disease. |
| – Neuroborreliosis | Ceftriaxone 50–75 mg/kg IV q24h OR penicillin G 300,000 U/kg/day IV div q4h; for 14–28 days (AIII) | |
| **Melioidosis** (*Burkholderia pseudomallei*)[309,310] | Acute sepsis: meropenem 75 mg/kg/day div q8h; OR ceftazidime 150 mg/kg/day IV div q8h; followed by TMP/SMX (10 mg/kg/day of TMP) PO div bid for 3–6 mo | Alternative convalescent therapy: amox/clav (90 mg/kg/day amox div tid, not bid) for children ≤7 y, or doxycycline for children >7 y; for 20 wk (AII) |
| **Mycobacteria, nontuberculous**[9,11–12,311] | | |
| – Adenitis in normal host (See Adenitis entries in this table and Table 6A.) | Excision usually curative (BII); azithromycin PO OR clarithromycin PO for 6–12 wk (with or without rifampin) if susceptible (BII) | Antibiotic susceptibility patterns are quite variable; cultures should guide therapy; medical therapy 60%–70% effective. Newer data suggest toxicity of antimicrobials may not be worth the small clinical benefit. |

## L. MISCELLANEOUS SYSTEMIC INFECTIONS (continued)

| Clinical Diagnosis | Therapy (evidence grade) | Comments |
|---|---|---|
| – Pneumonia or disseminated infection in compromised hosts (HIV or gamma-interferon receptor deficiency)[11,311] | Usually treated with 3 or 4 active drugs (eg, clarithromycin OR azithromycin, AND amikacin, cefoxitin, meropenem). Also test for ciprofloxacin, TMP/SMX, ethambutol, rifampin, linezolid, clofazimine, and doxycycline (BII). | See Chapter 11 for dosages; cultures are essential, as the susceptibility patterns of nontuberculous mycobacteria are varied. |
| **Nocardiosis** (*Nocardia asteroides* and *Nocardia brasiliensis*)[312,313] | TMP/SMX 8 mg/kg/day TMP div bid or sulfisoxazole 120–150 mg/kg/day PO div qid for 6–12 wk or longer. For severe infection, particularly in immunocompromised hosts, use ceftriaxone or imipenem AND amikacin 15–20 mg/kg/day IM, IV div q8h (AIII). | Wide spectrum of disease from skin lesions to brain abscess<br>Surgery when indicated<br>Alternatives: doxycycline (for children >7 y), amox/clav, or linezolid |
| **Plague** ***(Yersinia pestis)***[314–316] | Gentamicin 7.5 mg/kg/day IV div q8h (AII) | Doxycycline 4 mg/kg/day (max 200 mg/day) PO div bid or ciprofloxacin 30 mg/kg/day PO div bid |
| **Q fever** **(*Coxiella burnetii*)**[317,318] | Acute stage: doxycycline 4.4 mg/kg/day (max 200 mg/day) PO div bid for 14 days (AII) for children of any age.<br>Endocarditis and chronic disease (ongoing symptoms for 6–12 mo): doxycycline for children >7 y AND hydroxychloroquine for 18–36 mo (AIII).<br>Seek advice from pediatric infectious disease specialist for children ≤7 y: may require TMP-SMX, 8–10 mg TMP/kg/day div q12h with doxycycline; or levofloxacin with rifampin for 18 mo. | Follow doxycycline and hydroxychloroquine serum concentrations during endocarditis/chronic disease therapy.<br>CNS: Use fluoroquinolone (no prospective data) (BIII).<br>Clarithromycin may be an alternative based on limited data (CIII). |
| **Rocky Mountain spotted fever** (fever, petechial rash with centripetal spread; *Rickettsia rickettsii*)[319,320] | Doxycycline 4.4 mg/kg/day (max 200 mg/day) PO div bid for 7–10 days (AI) for children of any age | Start empiric therapy early. |
| **Tetanus** **(*Clostridium tetani*)**[321,322] | Metronidazole 30 mg/kg/day IV, PO div q8h or penicillin G 100,000 U/kg/day IV div q6h for 10–14 days AND TIG 3,000–6,000 U IM (AII) | Wound debridement essential; IVIG may provide antibody to toxin if TIG not available.<br>Immunize with Td or Tdap. |

| | | |
|---|---|---|
| | | See Chapter 14 for prophylaxis recommendations. |
| **Toxic shock syndrome** (toxin-producing strains of *S aureus* [including MRSA] or group A streptococcus)[6,7,323,324] | Empiric: vancomycin 45 mg/kg/day IV div q8h AND oxacillin/nafcillin 150 mg/kg/day IV div q6h, AND clindamycin 30–40 mg/kg/day div q8h ± gentamicin for 7–10 days (AIII) | Clindamycin added for the initial 48–72 h of therapy to decrease toxin production.<br>IVIG may provide additional benefit by binding circulating toxin (CIII).<br>For MSSA: oxacillin/nafcillin AND clindamycin ± gentamicin.<br>For CA-MRSA: vancomycin AND clindamycin ± gentamicin.<br>For group A streptococcus: penicillin G AND clindamycin. |
| **Tularemia (*Francisella tularensis*)**[152,325] | Gentamicin 6–7.5 mg/kg/day IM, IV div q8h; for 10–14 days (AII) | Alternatives: doxycycline (for 14–21 days) or ciprofloxacin (for 10 days) |

## 7. Preferred Therapy for Specific Bacterial and Mycobacterial Pathogens

### NOTES

- For fungal, viral, and parasitic infections, see chapters 8, 9, and 10, respectively.
- Limitations of space do not permit listing of all possible alternative antimicrobials.
- **Abbreviations:** amox/clav, amoxicillin/clavulanate (Augmentin); amp/sul, ampicillin/sulbactam (Unasyn); CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus;* CDC, Centers for Disease Control and Prevention; CNS, central nervous system; ESBL, extended spectrum beta-lactamase; FDA, US Food and Drug Administration; HRSA, Health Resources and Services Administration; IM, intramuscular; IV, intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; MDR, multidrug resistant; MIC, minimal inhibitory concentration; MRSA, methicillin-resistant *S aureus;* MSSA, methicillin-susceptible *S aureus;* NARMS, National Antimicrobial Resistance Monitoring System for Enteric Bacteria; pen-S, penicillin-susceptible; pip/tazo, piperacillin/tazobactam (Zosyn); PO, oral; PZA, pyrazinamide; spp, species; ticar/clav, ticarcillin/clavulanate (Timentin); TMP/SMX, trimethoprim/sulfamethoxazole; UTI, urinary tract infection.

## A. COMMON BACTERIAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIBIOTICS (GRAM POSITIVE)

| | Commonly Used Antibiotics (One Agent per Class Listed) | | | |
|---|---|---|---|---|
| | **Penicillin** | **Ampicillin/ Amoxicillin** | **Amoxicillin/ Clavulanate** | **Methicillin/ Oxacillin** |
| *Enterococcus faecalis*[a] | + | + | + | − |
| *Enterococcus faecium*[a] | + | + | + | − |
| *Staphylococcus,* coagulase negative +/- | − | − | − | +/− |
| *Staphylococcus aureus,* methicillin-resistant | − | − | − | − |
| *Staphylococcus aureus,* methicillin-susceptible | − | − | − | ++ |
| *Streptococcus pneumoniae* | ++ | ++ | ++ | + |
| *Streptococcus pyogenes* | ++ | ++ | ++ | ++ |

NOTE: ++ = very active (>90% of isolates are susceptible in most locations); + = some decreased susceptibility (substantially less active in vitro or resistance in isolates between 10% and 30% in some locations); +/− = significant resistance (30%–80% in some locations); − = not likely to be effective.

[a] Need to add gentamicin or other aminoglycoside to ampicillin/penicillin or vancomycin for in vitro bactericidal activity.

| Commonly Used Antibiotics (One Agent per Class Listed) | | | | | |
|---|---|---|---|---|---|
| | | | | Approved for Adults Some Studies in Children | |
| Cefazolin/ Cephalexin | Vancomycin | Clindamycin | Linezolid | Daptomycin | Ceftaroline |
| − | + | − | + | ++ | − |
| − | + | − | + | + | − |
| +/− | ++ | + | ++ | ++ | ++ |
| − | ++ | + | ++ | ++ | ++ |
| ++ | ++ | + | ++ | ++ | ++ |
| ++ | ++ | ++ | ++ | ++ | ++ |
| ++ | ++ | ++ | ++ | ++ | ++ |

## B. COMMON BACTERIAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIBIOTICS (GRAM NEGATIVE)[a]

| | Commonly Used Antibiotics (One Agent per Class Listed) | | | | |
|---|---|---|---|---|---|
| | **Ampicillin/ Amoxicillin** | **Amoxicillin/ Clavulanate** | **Cefazolin/ Cephalexin** | **Cefuroxime** | **Ceftriaxone/ Cefotaxime** |
| *Acinetobacter* spp | − | − | − | − | + |
| *Citrobacter* spp | − | − | − | + | + |
| *Enterobacter* spp[b] | − | − | − | +/− | + |
| *Escherichia coli*[c] | +/− | + | + | ++[d] | ++[d] |
| *Haemophilus influenzae*[f] | ++ | ++ | ++ | ++ | ++ |
| *Klebsiella* spp[c] | − | − | + | ++ | ++ |
| *Neisseria meningitidis* | ++ | ++ | 0 | ++ | ++ |
| *Pseudomonas aeruginosa* | − | − | − | − | − |
| *Salmonella*, non-typhoid spp | + | ++ | 0 | 0 | ++ |
| *Serratia* spp[b] | − | − | − | +/− | + |
| *Shigella* spp | + | + | 0 | + | ++ |
| *Stenotrophomonas maltophilia* | − | − | − | − | − |

NOTE: ++ = very active (>90% of isolates are susceptible in most locations); + = some decreased susceptibility (substantially less active in vitro or resistance in isolates between 10% and 30% in some locations); +/− = significant resistance (30%–80% in some locations); − = not likely to be effective; 0 = not usually tested for susceptibility for treatment of infections (resistant or has not previously been considered for routine therapy, so little data exist).

[a] CDC (NARMS) statistics and SENTRY surveillance system (JMI Laboratories) as primary references; also using current antibiograms from Children's Medical Center, Dallas, TX, and Rady Children's Hospital San Diego to assess pediatric trends. When sufficient data are available, pediatric community isolate susceptibility data are used. Nosocomial resistance patterns may be quite different, usually with increased resistance, particularly in adults; please check your local/regional hospital antibiogram for your local susceptibility patterns.

[b] AmpC will be constitutively produced in low frequency in every population of organisms and will be selected out during therapy with third-generation cephalosporins if used as single agent therapy.

[c] Rare carbapenem-resistant isolates in pediatrics (KPC, NDM strains).

[d] Will be resistant to virtually all current cephalosporins if ESBL producing.

[e] Follow the MIC, not the report for susceptible (S), intermediate (I), or resistant (R), as some ESBL producers will have low MICs and can be effectively treated with higher dosages.

[f] Will be resistant to ampicillin/amoxicillin if beta-lactamase producing.

| Commonly Used Antibiotics (One Agent per Class Listed) | | | | | | |
|---|---|---|---|---|---|---|
| Ceftazidime | Cefepime | Meropenem/ Imipenem | Piperacillin/ Tazobactam | TMP/ SMX | Ciprofloxacin | Gentamicin |
| + | + | ++ | + | + | + | ++ |
| + | ++ | ++ | + | ++ | ++ | ++ |
| + | ++ | ++ | + | + | ++ | ++ |
| ++[d] | ++[e] | ++ | ++ | + | ++ | ++ |
| ++ | ++ | ++ | ++ | ++ | ++ | +/− |
| ++ | ++[e] | ++ | ++ | ++ | ++ | ++ |
| + | ++ | ++ | ++ | 0 | ++ | 0 |
| + | ++ | ++ | ++ | − | ++ | + |
| ++ | ++ | ++ | ++ | ++ | ++ | 0 |
| + | ++ | ++ | + | ++ | ++ | ++ |
| ++ | ++ | ++ | ++ | +/− | ++ | 0 |
| + | +/− | +/− | + | ++ | ++ | +/− |

## C. COMMON BACTERIAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIBIOTICS (ANAEROBES)

| | Commonly Used Antibiotics (One Agent per Class Listed) | | | | |
|---|---|---|---|---|---|
| **Common Bacterial Pathogens: Anaerobes** | **Penicillin** | **Ampicillin/ Amoxicillin** | **Amoxicillin/ Clavulanate** | **Cefazolin** | **Cefoxitin** |
| Anaerobic streptococci | ++ | ++ | ++ | ++ | ++ |
| *Bacteroides fragilis* | +/− | +/− | ++ | − | + |
| *Clostridia* (eg, *tetani, perfringens*) | ++ | ++ | ++ | 0 | + |
| *Clostridium difficile* | − | − | − | 0 | − |

NOTE: ++ = very active (>90% of isolates are susceptible in most locations); + = some decreased susceptibility (substantially less active in vitro or resistance in isolates between 10% and 30% in some locations); +/− = significant resistance (30%–80% in some locations); − = not likely to be effective; 0 = not usually tested for susceptibility for treatment of infections (resistant or has not previously been considered for routine therapy, so little data exist).

| Commonly Used Antibiotics (One Agent per Class Listed) | | | | | |
|---|---|---|---|---|---|
| **Ceftriaxone/ Cefotaxime** | **Meropenem/ Imipenem** | **Piperacillin/ Tazobactam** | **Metronidazole** | **Clindamycin** | **Vancomycin** |
| ++ | ++ | ++ | ++ | ++ | ++ |
| − | ++ | ++ | ++ | + | 0 |
| +/− | ++ | ++ | ++ | + | ++ |
| − | ++ | 0 | ++ | − | ++ |

## D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS

| Organism | Clinical Illness | Drug of Choice (evidence grade) | Alternatives |
|---|---|---|---|
| *Acinetobacter baumanii*[1–4] | Sepsis, meningitis, nosocomial pneumonia, wound infection | Meropenem (BIII) or other carbapenem | Use culture results to guide therapy: ceftazidime, amp/sul; pip/tazo; TMP/SMX; ciprofloxacin; tigecycline; colistin.<br>Watch for emergence of resistance *during* therapy, including to colistin.<br>Consider combination therapy for life-threatening infection.<br>Inhaled colistin for pneumonia caused by MDR strains (BIII). |
| *Actinomyces israelii*[5] | Actinomycosis (cervicofacial, thoracic, abdominal) | Penicillin G; ampicillin (CIII) | Amoxicillin; doxycycline; clindamycin; ceftriaxone; imipenem |
| *Aeromonas hydrophila*[6] | Diarrhea | Ciprofloxacin (CIII) | Azithromycin, cefepime, TMP/SMX |
| | Sepsis, cellulitis, necrotizing fasciitis | Ceftazidime (BIII) | Cefepime; ceftriaxone, meropenem; ciprofloxacin |
| *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitan*[7] | Periodontitis, abscesses (including brain), endocarditis | Ampicillin (amoxicillin) ± gentamicin (CIII) | Doxycycline; TMP/SMX; ciprofloxacin; ceftriaxone |
| *Anaplasma* (formerly *Ehrlichia*) *phagocytophilum*[8,9] | Human granulocytic anaplasmosis | Doxycycline (all ages) (AII) | Rifampin, levofloxacin |
| *Arcanobacterium haemolyticum*[10] | Pharyngitis, cellulitis, Lemierre syndrome | Erythromycin; penicillin (BIII) | Azithromycin, amoxicillin, clindamycin; doxycycline; vancomycin |
| *Bacillus anthracis*[11] | Anthrax (cutaneous, gastrointestinal, inhalational, meningoencephalitis) | Ciprofloxacin (regardless of age) (AIII).<br>For invasive, systemic infection, use combination therapy. | Doxycycline; amoxicillin, levofloxacin, clindamycin; penicillin G; vancomycin, meropenem.<br>Bioterror strains may be antibiotic resistant. |

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| *Bacillus cereus* or *subtilis*[12,13] | Sepsis; toxin-mediated gastroenteritis | Vancomycin (BIII) | Ciprofloxacin, linezolid, daptomycin, clindamycin |
| *Bacteroides fragilis*[14,15] | Peritonitis, sepsis, abscesses | Metronidazole (AI) | Meropenem or imipenem (AI); ticar/clav; pip/tazo (AI); amox/clav (BII).<br>Recent surveillance suggests resistance of up to 25% for clindamycin. |
| *Bacteroides,* other spp[14,15] | Pneumonia, sepsis, abscesses | Metronidazole (BII) | Meropenem or imipenem; penicillin G or ampicillin if beta-lactamase negative |
| *Bartonella henselae*[16,17] | Cat-scratch disease | Azithromycin for lymph node disease (BII); gentamicin in combination with TMP/SMX AND rifampin for invasive disease (BIII) | Cefotaxime; ciprofloxacin; doxycycline |
| *Bartonella quintana*[18] | Bacillary angiomatosis, peliosis hepatis | Gentamicin plus doxycycline (BIII); erythromycin; ciprofloxacin (BIII) | Azithromycin; doxycycline |
| *Bordetella pertussis, parapertussis*[19,20] | Pertussis | Azithromycin (AIII); erythromycin (BII) | Clarithromycin; TMP/SMX; ampicillin |
| *Borrelia burgdorferi,* Lyme disease[21–23] | Treatment based on stage of infection (See Lyme disease in Chapter 6.) | Doxycycline if >7 y (AII); amoxicillin or cefuroxime in children ≤7 y (AIII); ceftriaxone IV for meningitis (AII) | |
| *Borrelia hermsii, turicatae, parkeri,* tick-borne relapsing fever[24,25] | Relapsing fever | Doxycycline for all ages (AIII) | Penicillin or erythromycin in children intolerant of doxycycline (BIII) |

## D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

| Organism | Clinical Illness | Drug of Choice (evidence grade) | Alternatives |
|---|---|---|---|
| *Borrelia recurrentis,* louse-borne relapsing fever[24,25] | Relapsing fever | Single-dose doxycycline for all ages (AIII) | Penicillin or erythromycin in children intolerant of doxycycline (BIII) |
| *Brucella* spp[26–28] | Brucellosis (See Chapter 6.) | Doxycycline AND rifampin (BIII); OR, for children ≤7 y: TMP/SMX AND rifampin (BIII) | For serious infection: doxycycline AND gentamicin AND rifampin; or TMP/SMX AND gentamicin AND rifampin (AIII). May require extended therapy (months). |
| *Burkholderia cepacia* complex[29–31] | Pneumonia, sepsis in immunocompromised children; pneumonia in children with cystic fibrosis[32] | Meropenem (BIII); for severe disease, ADD tobramycin AND TMP/SMX (AIII) | Imipenem, doxycycline; ceftazidime; pip/tazo; ciprofloxacin.<br>Aerosolized antibiotics may provide higher concentrations in lung.[31] |
| *Burkholderia pseudomallei*[33–35] | Melioidosis | Meropenem (AIII) or ceftazidime (BIII), followed by prolonged TMP/SMX for 12 wk (AII) | TMP/SMX, doxycycline, or amox/clav for chronic disease |
| *Campylobacter fetus*[36,37] | Sepsis, meningitis in the neonate | Meropenem (BIII) | Cefotaxime; gentamicin; erythromycin |
| *Campylobacter jejuni*[37–39] | Diarrhea | Azithromycin (BII); erythromycin (BII) | Doxycycline; ciprofloxacin (very high rates of ciprofloxacin-resistant strains in Thailand, Hong Kong, and Spain) |
| *Capnocytophaga canimorsus*[40,41] | Sepsis after dog bite (increased risk with asplenia) | Pip/tazo OR meropenem; amox/clav (BIII) | Clindamycin; linezolid; penicillin G; ciprofloxacin |
| *Capnocytophaga ochracea*[42] | Sepsis, abscesses | Clindamycin (BIII); amox/clav (BIII) | Meropenem; pip/tazo |

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| *Chlamydia trachomatis*[43–45] | Lymphogranuloma venereum | Doxycycline (AII) | Azithromycin; erythromycin |
| | Urethritis, cervicitis | Doxycycline (AII) | Azithromycin; erythromycin; ofloxacin |
| | Inclusion conjunctivitis of newborn | Azithromycin (AIII) | Erythromycin |
| | Pneumonia of infancy | Azithromycin (AIII) | Erythromycin; ampicillin |
| | Trachoma | Azithromycin (AI) | Doxycycline; erythromycin |
| *Chlamydophila* (formerly *Chlamydia*) *pneumoniae*[43,44,46,47] | Pneumonia | Azithromycin (AII); erythromycin (AII) | Doxycycline; ciprofloxacin |
| *Chlamydophila* (formerly *Chlamydia*) *psittaci*[48] | Psittacosis | Doxycycline for >7 y; azithromycin (AIII) OR erythromycin (AIII) for ≤7 y | Doxycycline, levofloxacin |
| *Chromobacterium violaceum*[49,50] | Sepsis, pneumonia, abscesses | Meropenem AND ciprofloxacin (AIII) | Imipenem, TMP/SMX |
| *Citrobacter koseri* (formerly *diversus*) and *freundii*[51–53] | Meningitis, sepsis | Meropenem (AIII) for ampC beta-lactamase resistance | Cefepime; ciprofloxacin; pip/tazo; ceftriaxone AND gentamicin; TMP/SMX<br>Carbapenem-resistant strains now reported |

## D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

| Organism | Clinical Illness | Drug of Choice (evidence grade) | Alternatives |
|---|---|---|---|
| *Clostridium botulinum*[54–56] | Botulism: foodborne; wound; potentially bioterror related | Botulism antitoxin heptavalent (equine) types A–G FDA approved in 2013 (www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM345147.pdf; accessed August 27, 2015)<br>No antibiotic treatment | For more information, call your state health department or the CDC Emergency Operations Center, 770/488-7100 (www.bt.cdc.gov/agent/Botulism/clinicians/treatment.asp; accessed August 27, 2015). |
| | Infant botulism | Human botulism immune globulin for infants (BabyBIG) (AII)<br>No antibiotic treatment | BabyBIG available nationally from the California Department of Public Health at 510/231-7600 (www.infantbotulism.org; accessed August 27, 2015) |
| *Clostridium difficile*[57,58] | Antibiotic-associated colitis (See Chapter 6, Table 6H, Gastrointestinal Infections, *Clostridium difficile*.) | Metronidazole PO (AI) | Vancomycin PO for metronidazole failures; stop the predisposing antimicrobial therapy, if possible.<br>No pediatric data on fidaxomicin PO.<br>No pediatric data on fecal transplantation for recurrent disease. |
| *Clostridium perfringens*[59,60] | Gas gangrene/necrotizing fasciitis/sepsis (also caused by *C sordellii, C septicum, C novyi*)<br>Food poisoning | Penicillin G AND clindamycin for invasive infection (BII); no antimicrobials indicated for foodborne illness | Meropenem, metronidazole, clindamycin monotherapy |

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| *Clostridium tetani*[61,62] | Tetanus | Metronidazole (AIII); penicillin G (BIII) | Treatment: tetanus immune globulin 3,000 to 6,000 U IM, with part injected directly into the wound.<br>Prophylaxis for contaminated wounds: 250 U IM for those with <3 tetanus immunizations.<br>Start/continue immunization for tetanus.<br>Alternative antibiotics: meropenem; doxycycline, clindamycin. |
| *Corynebacterium diphtheriae*[63] | Diphtheria | Diphtheria equine antitoxin (available through CDC under an investigational protocol [www.cdc.gov/diphtheria/dat.html]) AND erythromycin or penicillin G (AIII) | Antitoxin from the CDC Emergency Operations Center, 770/488-7100; protocol: www.cdc.gov/diphtheria/downloads/protocol.pdf (accessed August 27, 2015) |
| *Corynebacterium jeikeium*[64] | Sepsis, endocarditis | Vancomycin (AIII) | Penicillin G AND gentamicin, tigecycline, linezolid, daptomycin |
| *Corynebacterium minutissimum*[65,66] | Erythrasma; bacteremia in compromised hosts | Erythromycin PO for erythrasma (BIII); vancomycin IV for bacteremia (BIII) | Topical clindamycin for cutaneous infection |
| *Coxiella burnetii*[67,68] | Q fever (See Chapter 6, Table 6L, Q fever.) | Acute infection: doxycycline (all ages) (AII)<br>Chronic infection: TMP/SMX AND doxycycline (BII); OR levofloxacin AND rifampin | Alternative for acute infection: TMP/SMX |
| *Ehrlichia chaffeensis*[8,9]<br>*Ehrlichia muris*-like[69] | Human monocytic ehrlichiosis | Doxycycline (all ages) (AII) | Rifampin |
| *Ehrlichia ewingii*[8,9] | *E ewingii* ehrlichiosis | Doxycycline (all ages) (AII) | Rifampin |
| *Eikenella corrodens*[70] | Human bite wounds; abscesses, meningitis, endocarditis | Ampicillin; penicillin G (BIII) | Amox/clav; ticar/clav; pip/tazo; amp/sul; ceftriaxone; ciprofloxacin; imipenem<br>Resistant to clindamycin, cephalexin, erythromycin |

## D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

| Organism | Clinical Illness | Drug of Choice (evidence grade) | Alternatives |
|---|---|---|---|
| *Elizabethkingia* (formerly *Chryseobacterium*) *meningoseptica*[71,72] | Sepsis, meningitis | Levofloxacin; TMP/SMX (BIII) | Add rifampin to another active drug; pip/tazo. |
| *Enterobacter* spp[53,73,74] | Sepsis, pneumonia, wound infection, UTI | Cefepime; meropenem; pip/tazo (BII) | Ertapenem; imipenem; cefotaxime or ceftriaxone AND gentamicin; TMP/SMX; ciprofloxacin<br>Newly emerging carbapenem-resistant strains worldwide[74,75] |
| *Enterococcus* spp[76–78] | Endocarditis, UTI, intra-abdominal abscess | Ampicillin AND gentamicin (AI) | Vancomycin AND gentamicin.<br>For vancomycin-resistant strains that are also ampicillin resistant: linezolid and daptomycin show in vitro susceptibility. |
| *Erysipelothrix rhusiopathiae*[79] | Cellulitis (erysipeloid), sepsis, abscesses, endocarditis | Ampicillin (BIII); penicillin G (BIII) | Ceftriaxone; clindamycin, meropenem; amoxicillin, ciprofloxacin, erythromycin<br>Resistant to vancomycin, daptomycin, TMP/SMX |
| *Escherichia coli*<br>See Chapter 6 for specific infection entities and references.<br>*Increasing resistance to 3rd-generation cephalosporins due to ESBLs.* | UTI, community acquired, not hospital acquired | A 2nd- or 3rd-generation cephalosporin PO, IM as empiric therapy (BI) | Amoxicillin; TMP/SMX if susceptible. Ciprofloxacin if resistant to other options.<br>For hospital-acquired UTI, review hospital antibiogram for choices. |
| | Traveler's diarrhea | Azithromycin (AII) | Rifaximin (for nonfebrile, non-bloody diarrhea for children >11 y); cefixime |
| | Sepsis, pneumonia, hospital-acquired UTI | A 2nd- or 3rd-generation cephalosporin IV (BI) | For ESBL-producing strains: meropenem (AIII) or other carbapenem; pip/tazo and ciprofloxacin if resistant to other antibiotics. |
| | Meningitis | Ceftriaxone; cefotaxime (AIII) | For ESBL-producing strains: meropenem (AIII) |
| *Francisella tularensis*[80,81] | Tularemia | Gentamicin (AII) | Doxycycline; ciprofloxacin |

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| *Fusobacterium* spp[82,83] | Sepsis, soft tissue infection, Lemierre syndrome | Metronidazole (AIII); clindamycin (BIII) | Penicillin G; meropenem; pip/tazo |
| *Gardnerella vaginalis*[48,84] | Bacterial vaginosis | Metronidazole (BII) | Tinidazole; clindamycin; metronidazole gel; clindamycin cream |
| *Haemophilus* (now *Aggregatibacter*) *aphrophilus*[85] | Sepsis, endocarditis, abscesses (including brain abscess) | Ceftriaxone (AII); OR ampicillin AND gentamicin (BII) | Ciprofloxacin, amox/clav (for strains resistant to ampicillin) |
| *Haemophilus ducreyi*[48] | Chancroid | Azithromycin (AIII); ceftriaxone (BIII) | Erythromycin; ciprofloxacin |
| *Haemophilus influenzae*[86] | Nonencapsulated strains: Upper respiratory tract infections | Beta-lactamase negative: ampicillin IV (AI); amoxicillin PO (AI)<br>Beta-lactamase positive: ceftriaxone IV, IM (AI), or cefotaxime IV (AI); amox/clav (AI) OR 2nd- or 3rd-generation cephalosporins PO (AI) | Levofloxacin; azithromycin; TMP/SMX |
| | Type b strains: Meningitis, arthritis, cellulitis, epiglottitis, pneumonia | Beta-lactamase negative: ampicillin IV (AI); amoxicillin PO (AI)<br>Beta-lactamase positive: ceftriaxone IV, IM (AI), or cefotaxime IV (AI); amox/clav (AI) OR 2nd- or 3rd-generation cephalosporins PO (AI) | Full IV course (10 days) for meningitis, but oral step-down therapy well documented after response to treatment for non-CNS infections. |
| *Helicobacter pylori*[87,88] | Gastritis, peptic ulcer | Clarithromycin AND amoxicillin AND omeprazole (AII) | Other regimens include metronidazole (especially for concerns of clarithromycin resistance)[89] and other proton-pump inhibitors. |
| *Kingella kingae*[90,91] | Osteomyelitis, arthritis | Ampicillin; penicillin G (AII) | Ceftriaxone; TMP/SMX; cefuroxime; ciprofloxacin |

## D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

| Organism | Clinical Illness | Drug of Choice (evidence grade) | Alternatives |
|---|---|---|---|
| *Klebsiella* spp (*K pneumoniae*, K oxytoca)[92–94] | UTI | A 2nd- or 3rd-generation cephalosporin (AII) | Use most narrow spectrum agent active against pathogen: TMP/SMX; ciprofloxacin, gentamicin.<br>ESBL producers should be treated with a carbapenem (meropenem, ertapenem, imipenem), but KPC (carbapenemase)-containing bacteria may require ciprofloxacin, colistin.[94] |
| | Sepsis, pneumonia, meningitis | Ceftriaxone; cefotaxime, cefepime (AIII) | Carbapenem or ciprofloxacin if resistant to other routine antibiotics.<br>Meningitis caused by ESBL producer: meropenem.<br>KPC carbapenemase producers: ciprofloxacin, colistin, OR ceftazidime/avibactam, just approved by FDA for adults in 2015, and should be active against current strains of KPC *Klebsiella*. |
| *Klebsiella granulomatis*[48] | Granuloma inguinale | Azithromycin (AII) | Doxycycline; TMP/SMX; ciprofloxacin |
| *Legionella* spp[95] | Legionnaires disease | Azithromycin (AI) OR levofloxacin (AII) | Erythromycin, TMP/SMX, doxycycline |
| *Leptospira* spp[96] | Leptospirosis | Penicillin G IV (AII); ceftriaxone IV (AII) | Amoxicillin; doxycycline; azithromycin |
| *Leuconostoc*[97] | Bacteremia | Penicillin G (AIII); ampicillin (BIII) | Clindamycin; erythromycin; doxycycline (resistant to vancomycin) |
| *Listeria monocytogenes*[98] | Sepsis, meningitis in compromised host; neonatal sepsis | Ampicillin (ADD gentamicin for severe infection.) (AII) | Ampicillin AND TMP/SMX; ampicillin AND linezolid |
| *Moraxella catarrhalis*[99] | Otitis, sinusitis, bronchitis | Amox/clav (AI) | TMP/SMX; a 2nd- or 3rd-generation cephalosporin |
| *Morganella morganii*[100,101] | UTI, sepsis, wound infection | Cefepime (AIII); meropenem (AIII) | Pip/tazo; ceftriaxone AND gentamicin; ciprofloxacin |

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| *Mycobacterium abscessus*[102,103] | Skin and soft tissue infections; pneumonia in cystic fibrosis | Clarithromycin or azithromycin (AIII); ADD amikacin ± cefoxitin for invasive disease (AIII). | Also test for susceptibility to meropenem, tigecycline, linezolid. May need pulmonary resection. |
| *Mycobacterium avium* complex[102,104] | Cervical adenitis | Clarithromycin (AII); azithromycin (AII) | Surgical excision is more likely to lead to cure than sole medical therapy.<br>May increase cure rate with addition of rifampin or ethambutol. |
| | Pneumonia | Clarithromycin (AII) or azithromycin (AII) AND ethambutol ± rifampin | Depending on susceptibilities and the severity of illness, ADD amikacin ± ciprofloxacin. |
| | Disseminated disease in competent host, or disease in immunocompromised host | Clarithromycin or azithromycin AND ethambutol AND rifampin (AIII) | Depending on susceptibilities and the severity of illness, ADD amikacin ± ciprofloxacin. |
| *Mycobacterium bovis*[105,106] | Tuberculosis (adenitis; abdominal tuberculosis; meningitis) | Isoniazid AND rifampin (AII); add ethambutol for suspected resistance (AIII). | Add streptomycin for severe infection.<br>*M bovis* is always resistant to PZA. |
| *Mycobacterium chelonae*[102,104,107,108] | Abscesses; catheter infection | Clarithromycin or azithromycin (AIII); ADD amikacin ± cefoxitin for invasive disease (AIII). | Also test for susceptibility to cefoxitin; TMP/SMX; doxycycline; tobramycin, imipenem; moxifloxacin, linezolid. |
| *Mycobacterium fortuitum* complex[102,108] | Skin and soft tissue infections; catheter infection | Amikacin AND meropenem (AIII) ± ciprofloxacin (AIII) | Also test for susceptibility to clarithromycin, cefoxitin; sulfonamides; doxycycline; linezolid. |
| *Mycobacterium leprae*[109] | Leprosy | Dapsone AND rifampin for paucibacillary (1–5 patches) (AII).<br>ADD clarithromycin (or clofazimine) for lepromatous, multibacillary (>5 patches) disease (AII). | Consult HRSA (National Hansen's Disease [Leprosy] Program) at www.hrsa.gov/hansensdisease for advice about treatment and free antibiotics: 800/642-2477 (accessed August 27, 2015). |

## D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

| Organism | Clinical Illness | Drug of Choice (evidence grade) | Alternatives |
|---|---|---|---|
| *Mycobacterium marinum/ balnei*[102,110] | Papules, pustules, abscesses (swimmer's granuloma) | Clarithromycin ± rifampin (AIII) | TMP/SMX AND rifampin; doxycycline |
| *Mycobacterium tuberculosis*[105,111] See Tuberculosis in Chapter 6, Table 6F, Lower Respiratory Tract Infections, for detailed recommendations for active infection, latent infection, and exposures in high-risk children. | Tuberculosis (pneumonia; meningitis; cervical adenitis; mesenteric adenitis; osteomyelitis) | For active infection: isoniazid AND rifampin AND PZA (AI)<br>For latent infection: isoniazid daily, biweekly, or in combination with rifapentine once weekly (AII) | Add ethambutol for suspect resistance; add streptomycin for severe infection.<br>For MDR tuberculosis, bedaquiline is now FDA approved for adults and available for children.<br>Corticosteroids should be added to regimens for meningitis, mesenteric adenitis, and endobronchial infection (AIII). |
| *Mycoplasma hominis*[112,113] | Nongonococcal urethritis; neonatal infection including meningitis | Clindamycin (AIII) | Fluoroquinolones; doxycycline<br>Usually erythromycin resistant |
| *Mycoplasma pneumoniae*[114] | Pneumonia | Azithromycin (AI); erythromycin (BI); macrolide resistance emerging worldwide[115] | Doxycycline and fluoroquinolones are active against macrolide-susceptible and macrolide-resistant strains. |
| *Neisseria gonorrhoeae*[48] | Gonorrhea; arthritis | Ceftriaxone AND azithromycin or doxycycline (AIII) | Oral cefixime as single drug therapy no longer recommended due to increasing resistance[116]<br>Spectinomycin IM |
| *Neisseria meningitidis*[117,118] | Sepsis, meningitis | Ceftriaxone (AI); cefotaxime (AI) | Penicillin G or ampicillin if susceptible<br>For prophylaxis following exposure: rifampin or ciprofloxacin (ciprofloxacin-resistant strains have now been reported). Azithromycin may be less effective. |

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| *Nocardia asteroides* or *brasiliensis*[119,120] | Nocardiosis | TMP/SMX (AII); sulfisoxazole (BII); imipenem AND amikacin for severe infection (AII) | Linezolid, ceftriaxone; clarithromycin, minocycline; levofloxacin, tigecycline, amox/clav |
| *Oerskovia* (now known as *Cellulosimicrobium cellulans*)[121] | Wound infection; catheter infection | Vancomycin ± rifampin (AIII) | Linezolid; resistant to beta-lactams, macrolides, clindamycin, aminoglycosides |
| *Pasteurella multocida*[122] | Sepsis, abscesses, animal bite wound | Penicillin G (AIII); ampicillin (AIII); amoxicillin (AIII) | Amox/clav; ticar/clav; pip/tazo; doxycycline; ceftriaxone; cefpodoxime; cefuroxime, TMP/SMX. Cephalexin may not demonstrate adequate activity. Not usually susceptible to clindamycin. |
| *Peptostreptococcus*[123] | Sepsis, deep head/neck space and intra-abdominal infection | Penicillin G (AII); ampicillin (AII) | Clindamycin; vancomycin; meropenem, imipenem, metronidazole |
| *Plesiomonas shigelloides*[124,125] | Diarrhea, neonatal sepsis, meningitis | Antibiotics may not be necessary to treat diarrhea: 2nd- and 3rd-generation cephalosporins (AIII); azithromycin (BIII); ciprofloxacin (CIII). For meningitis/sepsis: ceftriaxone. | Meropenem; TMP/SMX, amox/clav |
| *Prevotella* (*Bacteroides*) spp,[126] *melaninogenica* | Deep head/neck space abscess; dental abscess | Metronidazole (AII); meropenem or imipenem (AII) | Pip/tazo; clindamycin |
| *Propionibacterium acnes*[127,128] | In addition to acne, invasive infection: sepsis, post-op wound infection | Penicillin G (AIII); vancomycin (AIII) | Cefotaxime; ceftriaxone, doxycycline; clindamycin; linezolid, daptomycin |

## D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

| Organism | Clinical Illness | Drug of Choice (evidence grade) | Alternatives |
|---|---|---|---|
| *Proteus mirabilis*[129] | UTI, sepsis, meningitis | Ceftriaxone (AII) or cefotaxime (AII); cefepime; ciprofloxacin; gentamicin | Carbapenem; pip/tazo; increasing resistance to ampicillin, TMP/SMX, and fluoroquinolones, particularly in nosocomial isolates<br>Colistin resistant |
| *Proteus vulgaris,* other spp (indole-positive strains)[53] | UTI, sepsis, meningitis | Cefepime; ciprofloxacin; gentamicin (BIII) | Meropenem or other carbapenem; pip/tazo; TMP/SMX<br>Colistin resistant |
| *Providencia* spp[53,74,130] | Sepsis | Cefepime; ciprofloxacin, gentamicin (BIII) | Meropenem or other carbapenem; pip/tazo; TMP/SMX<br>Colistin resistant |
| *Pseudomonas aeruginosa*[74,131–135] | UTI | Cefepime (AII); other antipseudomonal beta-lactams | Tobramycin; amikacin; ciprofloxacin |
| | Nosocomial sepsis, pneumonia | Cefepime (AI) or meropenem (AI); OR pip/tazo AND tobramycin (BI); ceftazidime AND tobramycin (BII) | Ciprofloxacin AND tobramycin.<br>Controversy regarding additional clinical benefit in outcomes using newer, more potent beta-lactams over aminoglycoside combinations, but combinations may decrease emergence of resistance.<br>Ceftolozane/tazobactam was just approved by FDA for adults in 2015 and may be active against otherwise resistant strains. |
| | Pneumonia in cystic fibrosis[136–138]<br>See Cystic Fibrosis in Chapter 6, Table 6F, Lower Respiratory Tract Infections. | Cefepime (AII) or meropenem (AI); OR ceftazidime AND tobramycin (BII); ADD aerosol tobramycin (AI).<br>Azithromycin provides benefit in prolonging interval between exacerbations. | Inhalational antibiotics for prevention of acute exacerbations: tobramycin, aztreonam, colistin.<br>Many organisms are multidrug resistant; consider ciprofloxacin or colistin parenterally; in vitro synergy testing may suggest effective combinations.[138]<br>For multidrug-resistant organisms, colistin aerosol (AIII). |
| *Pseudomonas cepacia, mallei,* or *pseudomallei* (See Burkholderia.) | | | |

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| *Rhodococcus equi*[139] | Necrotizing pneumonia | Imipenem AND vancomycin (AIII) | Dual drug combination therapy with ciprofloxacin AND azithromycin or rifampin |
| *Rickettsia*[68,140,141] | Rocky Mountain spotted fever, Q fever, typhus, rickettsial pox | Doxycycline (all ages) (AII) | Chloramphenicol is less effective than doxycycline. |
| *Salmonella*, non-*typhi*[142–144] | Gastroenteritis (may not require therapy if clinically improving and not immunocompromised or <1 y); focal infections; bacteremia | Ceftriaxone (AII); cefixime (AII); azithromycin (AII) | For susceptible strains: ciprofloxacin; TMP/SMX; ampicillin; resistance to fluoroquinolones detected by nalidixic acid testing |
| *Salmonella typhi*[142,145] | Typhoid fever | Azithromycin (AII); ceftriaxone (AII); ciprofloxacin (AII) | For susceptible strains: TMP/SMX; ampicillin |
| *Serratia marcescens*[53,74] | Nosocomial sepsis, pneumonia | A carbapenem (AII) | Pip/tazo; cefepime if susceptible; ceftriaxone or cefotaxime AND gentamicin; or ciprofloxacin<br>Resistant to colistin |
| *Shewanella* spp[146] | Wound infection, nosocomial pneumonia, peritoneal-dialysis peritonitis, ventricular shunt infection, neonatal sepsis | Ceftazidime (AIII); gentamicin (AIII) | Ampicillin, meropenem, pip/tazo, ciprofloxacin |
| *Shigella* spp[147,148] | Enteritis, UTI, prepubertal vaginitis | Ceftriaxone (AII); azithromycin[149] (AII); cefixime (AII); ciprofloxacin[150] (AII) | Resistance to azithromycin now reported. Use most narrow-spectrum agent active against pathogen: ampicillin (not amoxicillin for enteritis); TMP/SMX. |
| *Spirillum minus*[151,152] | Rat-bite fever (sodoku) | Penicillin G IV (AII); for endocarditis, ADD gentamicin or streptomycin (AIII). | Ampicillin; doxycycline; cefotaxime, vancomycin, streptomycin |

## D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

| Organism | Clinical Illness | Drug of Choice (evidence grade) | Alternatives |
|---|---|---|---|
| *Staphylococcus aureus* (See chapters 4 and 6 for specific infections.)[153,154] | | | |
| – Mild–moderate infections | Skin infections, mild–moderate | MSSA: a 1st-generation cephalosporin (cefazolin IV, cephalexin PO) (AI); oxacillin/nafcillin IV (AI), dicloxacillin PO (AI)<br>MRSA: vancomycin IV, or clindamycin IV or PO (if susceptible), or TMP/SMX PO (AII) | For MSSA: amox/clav<br>For CA-MRSA: linezolid IV, PO; daptomycin IV |
| – Moderate–severe infections, treat empirically for CA-MRSA. | Pneumonia, sepsis, myositis, osteomyelitis, etc | MSSA: oxacillin/nafcillin IV (AI); a 1st-generation cephalosporin (cefazolin IV) (AI) ± gentamicin (AIII)<br>MRSA: vancomycin (AII) or clindamycin (AII); ± gentamicin ± rifampin (AIII) | For CA-MRSA: linezolid (AII); OR daptomycin for non-pulmonary infection (AII) (studies underway in children); ceftaroline IV (studies underway in children)<br>Approved for adults in 2015: dalbavancin, oritavancin, tedizolid (See Chapter 4.) |
| *Staphylococcus,* coagulase negative[155,156] | Nosocomial bacteremia (neonatal bacteremia), infected intravascular catheters, CNS shunts, UTI | Vancomycin (AII) | If susceptible: nafcillin (or other anti-staph beta-lactam); rifampin (in combination); clindamycin, linezolid; ceftaroline IV (studies underway in children) |
| *Stenotrophomonas maltophilia*[157,158] | Sepsis | TMP/SMX (AII) | Ceftazidime; ticar/clav; doxycycline; levofloxacin |
| *Streptobacillus moniliformis*[151,152] | Rat-bite fever (Haverhill fever) | Penicillin G (AIII); ampicillin (AIII); for endocarditis, ADD gentamicin or streptomycin (AIII). | Doxycycline; ceftriaxone; carbapenems; clindamycin; vancomycin |

| | | | |
|---|---|---|---|
| *Streptococcus,* group A[159] | Pharyngitis, impetigo, adenitis, cellulitis, necrotizing fasciitis | Penicillin (AI); amoxicillin (AI) | A 1st-generation cephalosporin (cefazolin or cephalexin) (AI); clindamycin (AI); a macrolide (AI), vancomycin (AIII)<br>For recurrent streptococcal pharyngitis, clindamycin or amox/clav (AIII) |
| *Streptococcus,* group B[160] | Neonatal sepsis, pneumonia, meningitis | Penicillin (AII) or ampicillin (AII) | Gentamicin is used initially until group B strep has been identified as the cause of infection, and a clinical/microbiologic response has been documented (AIII). |
| *Streptococcus, milleri/ anginosus* group (*S intermedius, anginosus,* and *constellatus;* includes some beta-hemolytic group C and group G streptococci)[161–163] | Pneumonia, sepsis, skin and soft tissue infection, sinusitis,[164] arthritis, brain abscess, meningitis | Penicillin G (AIII); ampicillin (AIII); ADD gentamicin for serious infection (AIII).<br>Many strains show decreased susceptibility to penicillin, requiring higher dosages. | Ceftriaxone; clindamycin; vancomycin |
| *Streptococcus pneumoniae*[165–168]<br>With widespread use of conjugate pneumococcal vaccines, antibiotic resistance in pneumococci has decreased substantially.[168] | Sinusitis, otitis[165] | Amoxicillin, high-dose (90 mg/kg/day) (AII); new data suggests that standard dose (40–45 mg/kg/day) may again be effective.[168] | Amox/clav; cefdinir; cefpodoxime; cefuroxime; clindamycin; OR ceftriaxone IM |
| | Meningitis | Ceftriaxone (AI) or cefotaxime (AI); AND vancomycin for possible ceftriaxone-resistant strains (AIII) | Penicillin G alone for pen-S strains; ceftriaxone alone for ceftriaxone-susceptible strains |
| | Pneumonia,[114] osteomyelitis/arthritis, sepsis | Ampicillin (AII); ceftriaxone (AI); cefotaxime (AI) | Penicillin G for pen-S strains (AI) |

## D. PREFERRED THERAPY FOR SPECIFIC BACTERIAL AND MYCOBACTERIAL PATHOGENS (continued)

| Organism | Clinical Illness | Drug of Choice (evidence grade) | Alternatives |
|---|---|---|---|
| *Streptococcus,* viridans group (alpha-hemolytic streptococci, most commonly *S sanguis, S oralis* [*mitis*], *S salivarius, S mutans, S morbillorum*)[169] | Endocarditis | Penicillin G ± gentamicin (AII) OR ceftriaxone ± gentamicin (AII) | Vancomycin |
| *Treponema pallidum*[48,170] | Syphilis | Penicillin G (AII) | Desensitize to penicillin preferred to alternate therapies. Doxycycline; ceftriaxone. |
| *Ureaplasma urealyticum*[48,171] | Genitourinary infections | Azithromycin (AII) | Erythromycin; doxycycline, ofloxacin (for adolescent genital infections) |
| | Neonatal pneumonia (Therapy may not be effective.) | Azithromycin (AIII) | |
| *Vibrio cholerae*[172,173] | Cholera | Doxycycline (AI) or azithromycin (AII) | If susceptible: ciprofloxacin |
| *Vibrio vulnificus*[174,175] | Sepsis, necrotizing fasciitis | Doxycycline AND ceftazidime (AII) | Ciprofloxacin AND cefotaxime or ceftriaxone |
| *Yersinia enterocolitica*[176,177] | Diarrhea, mesenteric enteritis, reactive arthritis, sepsis | TMP/SMX for enteritis (AIII); ciprofloxacin or ceftriaxone for invasive infection (AIII) | Gentamicin, doxycycline |
| *Yersinia pestis*[178,179] | Plague | Gentamicin (AIII) | Levofloxacin; doxycycline; ciprofloxacin |
| *Yersinia pseudotuberculosis*[177,180] | Mesenteric adenitis; Far East scarlet fever; reactive arthritis | TMP/SMX (AIII) or ciprofloxacin (AIII) | Ceftriaxone; gentamicin, doxycycline |

## 8. Preferred Therapy for Specific Fungal Pathogens

### NOTES

- See Chapter 2 for discussion of the differences between polyenes, azoles, and echinocandins.
- **Abbreviations:** ABLC, amphotericin B lipid complex (Abelcet); AmB, amphotericin B; AmB-D, amphotericin B deoxycholate, the conventional standard AmB (original trade name Fungizone); bid, twice daily; CNS, central nervous system; CSF, cerebrospinal fluid; div, divided; ECMO, extracorporeal membrane oxygenation; HIV, human immunodeficiency virus; IV, intravenous; L-AmB, liposomal amphotericin B (AmBisome); PO, orally; qd, once daily; qid, 4 times daily; spp, species; TMP/SMX, trimethoprim/sulfamethoxazole.

## A. OVERVIEW OF FUNGAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIFUNGALS

| Fungal Species | Amphotericin B Formulations | Fluconazole | Itraconazole | Voriconazole | Posaconazole | Isavuconazole | Flucytosine | Caspofungin, Micafungin, or Anidulafungin |
|---|---|---|---|---|---|---|---|---|
| *Aspergillus calidoustus* | ++ | − | − | − | − | − | − | ++ |
| *Aspergillus fumigatus* | + | − | +/− | ++ | + | ++ | − | + |
| *Aspergillus terreus* | − | − | + | ++ | + | ++ | − | + |
| *Blastomyces dermatitidis* | ++ | + | ++ | + | + | + | − | − |
| *Candida albicans* | + | ++ | + | + | + | + | + | ++ |
| *Candida glabrata* | + | − | +/− | +/− | +/− | +/− | + | +/− |
| *Candida guilliermondii* | ++ | +/− | + | + | + | + | + | +/− |
| *Candida krusei* | + | − | − | + | + | + | + | ++ |
| *Candida lusitaniae* | − | ++ | + | + | + | + | + | + |
| *Candida parapsilosis* | ++ | ++ | + | + | + | + | + | +/− |
| *Candida tropicalis* | + | ++ | + | + | + | + | + | ++ |
| *Coccidioides immitis* | ++ | + | ++ | + | ++ | + | − | − |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *Cryptococcus* spp | ++ | + | + | + | + | + | ++ | − |
| *Fusarium* spp | +/− | − | − | ++ | + | + | − | − |
| *Histoplasma capsulatum* | ++ | + | ++ | + | + | + | − | − |
| *Mucor* spp | ++ | − | +/− | − | + | + | − | − |
| *Paracoccidioides* spp | + | + | ++ | + | + | + | − | − |
| *Penicillium* spp | +/− | − | ++ | + | + | + | − | − |
| *Rhizopus* spp | ++ | − | − | − | + | + | − | − |
| *Scedosporium apiospermum* | − | − | +/− | + | + | + | − | +/− |
| *Scedosporium prolificans* | − | − | +/− | +/− | +/− | +/− | − | +/− |
| *Sporothrix* spp | + | + | ++ | + | + | + | − | − |
| *Trichosporon* spp | − | + | + | ++ | + | + | − | − |

NOTE: ++ = preferred therapy(ies); + = usually active; +/− =variably active; − = usually not active.

## B. SYSTEMIC INFECTIONS

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| **Prophylaxis** | | |
| **Prophylaxis of invasive fungal infection in patients with hematologic malignancies**[1–11] | Fluconazole 6 mg/kg/day for prevention of infection (AII). Posaconazole for prevention of infection has been well studied in adults (AI) and offers anti-mold coverage.[4] | Fluconazole is not effective against molds and some strains of *Candida*. Posaconazole PO, voriconazole PO, and micafungin IV are effective in adults in preventing yeast and mold infections but are not well studied in children for this indication.[12] |
| **Prophylaxis of invasive fungal infection in patients with solid organ transplants**[13–17] | Fluconazole 6 mg/kg/day for prevention of infection (AII) | AmB, caspofungin, micafungin, voriconazole, or posaconazole may be effective in preventing infection. |
| **Treatment** | | |
| **Aspergillosis**[18–22] | Voriconazole 18 mg/kg/day IV div q12h for a loading dose on the first day, then 16 mg/kg/day IV div q12h as a maintenance dose for children 2–12 y. In children >12 y, use adult dosing (load 12 mg/kg/day IV div q12h on first day, then 8 mg/kg/day div q12h as a maintenance dose) (AII). When stable, may switch from voriconazole IV to voriconazole PO at a dose of 18 mg/kg/day div bid for children 2–12 y and at least 400 mg/day div bid for children >12 y (AIII). These are only initial dosing recommendations; continued dosing is guided by close monitoring of trough serum voriconazole concentrations. Voriconazole PO bioavailability in children is only approximately 50%, so trough levels are crucial at this stage.[23] | Voriconazole is the preferred primary antifungal therapy for all clinical forms of infection based on its years of experience. Early initiation of therapy is important while a diagnostic evaluation is conducted.<br>Optimal voriconazole trough serum concentrations (generally thought to be >2 µg/mL) are important for success. It is critical to monitor trough concentrations to guide therapy due to high inter-patient variability.[25] Low voriconazole concentrations are a leading cause of clinical failure. Younger children often have lower voriconazole levels and need higher dosing.<br>Total treatment course is at least 6–12 wk, largely dependent on the degree and duration of immunosuppression and evidence of disease improvement.<br>Salvage therapy options include a change of antifungal class (using L-AmB or an echinocandin), switching to isavuconazole, switching to posaconazole (trough concentrations >0.7 µg/mL), or using combination antifungal therapy. |

| | | |
|---|---|---|
| | Alternatives for primary therapy: L-AmB 5 mg/kg/day[24] (AII) or isavuconazole (AI). ABLC is another possible alternative. Echinocandin primary monotherapy should not be used (CII). | Careful consideration has to be used before beginning azole therapy after a patient has failed azole prophylaxis.<br>Combination antifungal therapy with voriconazole plus an echinocandin can be considered in select patients. The addition of anidulafungin to voriconazole as combination therapy found some statistical benefit to the combination over voriconazole monotherapy in certain patients.[26] In vitro data suggest some synergy with 2 (but not 3) drug combinations: an azole plus an echinocandin is the most well studied. If combination therapy is employed, this is likely best done initially when voriconazole trough concentrations may not be appropriate yet.<br>Azole-resistant *Aspergillus fumigatus* is increasing; confirm antifungal susceptibility in evaluating causes of clinical failure.<br>Micafungin likely has equal efficacy to caspofungin against aspergillosis.[27]<br>Return of immune function is paramount to treatment success; for children receiving corticosteroids, decreasing the corticosteroid dosage or changing to steroid-sparing protocols is also important. |
| ***Bipolaris, Cladophialophora, Curvularia, Exophiala,*** and other agents of **phaeohyphomycosis** (dematiaceous, pigmented fungi)[28–32] | Voriconazole 18 mg/kg/day IV div q12h for a loading dose on the first day, then 16 mg/kg/day IV div q12h as a maintenance dose for children 2–12 y. In children >12 y, use adult dosing (load 12 mg/kg/day IV div q12h on first day, then 8 mg/kg/day div q12h as a maintenance dose) (AII).<br>When stable, may switch from voriconazole IV to voriconazole PO at a dose of 18 mg/kg/day div bid for children 2–12 y and at least 400 mg/day div bid for children >12 y (AIII).<br>Alternatives could include posaconazole (trough concentrations >0.7 μg/mL) or combination therapy with an echinocandin and an azole or an echinocandin and AmB (AIII). | Surgery is essential; antifungal susceptibilities are variable.<br>Optimal voriconazole trough concentrations (generally thought to be >2 μg/mL) are important.<br>These can be highly resistant infections, so strongly recommend antifungal susceptibility testing and consultation with a pediatric infectious diseases expert. |

## B. SYSTEMIC INFECTIONS (continued)

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| **Blastomycosis** (North American)[33–38] | For moderate-severe disease: ABLC or L-AmB 5 mg/kg IV daily as 3–4 h infusion for 1–2 wk or until improvement noted, followed by oral solution itraconazole 10 mg/kg/day div bid (max 400 mg/day) PO for a total of 12 mo (AIII)<br>For mild-moderate disease: oral solution itraconazole 10 mg/kg/day div bid (max 400 mg/day) PO for a total of 6–12 mo (AIII) | Itraconazole oral solution provides greater and more reliable absorption than capsules; serum concentrations of itraconazole should be determined 2 wk after start of therapy to ensure adequate drug exposure (maintain trough concentrations at least >0.5 µg/mL).<br>Alternative to itraconazole: 12 mg/kg/day fluconazole (BIII) after a loading dose of 25 mg/kg/day.<br>Patients with extrapulmonary blastomycosis should receive at least 12 mo of total therapy.<br>CNS blastomycosis should begin with ABLC/L-AmB for 4–6 wk, followed by an azole (fluconazole preferred, at 12 mg/kg/day after a loading dose), for a total therapy of at least 12 mo and until resolution of CSF abnormalities.<br>Lifelong itraconazole if immunosuppression cannot be reversed. |
| **Candidiasis**[39–43] (See Chapter 2.) | | |
| – Disseminated infection | For neutropenic patients<br>An echinocandin is recommended. Caspofungin 70 mg/m$^2$ IV loading dose on day 1 (max dose 70 mg), followed by 50 mg/m$^2$ IV (max dose 70 mg) on subsequent days (AII); OR micafungin 2–4 mg/kg/day q24h (max dose 150 mg) (BIII).[44]<br>ABLC or L-AmB 5 mg/kg/day IV q24h (BII) is an effective but less attractive alternative due to potential toxicity.<br>Fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day) is an alternative for patients who are not critically ill and have had no prior azole exposure. For children on ECMO, 35 mg/kg load followed by 12 mg/kg/day is also likely to be beneficial. | Prompt removal of infected IV catheter or any infected devices is absolutely critical to success.<br>For infections with *C krusei* or *C glabrata,* an echinocandin is preferred; however, there are increasing reports of some *C glabrata* resistance to echinocandins (treatment would therefore be lipid formulation AmB).<br>Lipid formulation AmB (3–5 mg/kg daily) is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents. Transition from AmB to fluconazole is recommended after 5–7 days among patients who have isolates that are susceptible to fluconazole, who are clinically stable, and in whom repeat cultures on antifungal therapy are negative. |

For non-neutropenic patients

An echinocandin is recommended as initial therapy. Caspofungin 70 mg/m$^2$ IV loading dose on day 1 (max dose 70 mg), followed by 50 mg/m$^2$ IV (max dose 70 mg) on subsequent days (AII); OR micafungin 2–4 mg/kg/day q24h (max dose 150 mg) (BIII).[44]

Fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day) is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species. For children on ECMO, 35 mg/kg load followed by 12 mg/kg/day is also likely to be beneficial.

Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for non-neutropenic patients who are clinically stable, have isolates that are susceptible to fluconazole (eg, *C albicans*), and have negative repeat blood cultures following initiation of antifungal therapy.

For CNS infections

AmB-D (1 mg/kg/day) or L-AmB/ABLC (5 mg/kg/day) with or without flucytosine 100 mg/kg/day PO div q6h (AII) until initial clinical response, followed by step-down therapy with fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day); echinocandins do not achieve therapeutic concentrations in CSF.

Among patients with suspected azole- and echinocandin-resistant *Candida* infections, lipid formulation AmB (3–5 mg/kg/day) is recommended.

Voriconazole (18 mg/kg/day div q12h load, followed by 16 mg/kg/day div q12h) is effective for candidemia but offers little advantage over fluconazole as initial therapy. Voriconazole is recommended as step-down oral therapy for selected cases of candidemia due to *C krusei*.

Follow-up blood cultures should be performed every day or every other day to establish the time point at which candidemia has been cleared.

Duration of therapy is for 2 wk AFTER negative cultures in pediatric patients without obvious metastatic complications and after symptom resolution but 3 wk in neonates due to higher rate of meningitis and dissemination.

In neutropenic patients, ophthalmologic findings of choroidal and vitreal infection are minimal until recovery from neutropenia; therefore, dilated funduscopic examinations should be performed within the first week after recovery from neutropenia.

All non-neutropenic patients with candidemia should have a dilated ophthalmologic examination, preferably performed by an ophthalmologist, within the first week after diagnosis.

**B. SYSTEMIC INFECTIONS** (continued)

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| – Oropharyngeal, esophageal[39] | Oropharyngeal, mild disease: clotrimazole 10 mg troches PO 5 times daily OR nystatin 100,000 U/mL, 4–6 mL 4 times daily for 7–14 days; miconazole mucoadhesive buccal 50 mg tablet to the mucosal surface over the canine fossa once daily for 7–14 days; alternatives for mild disease include nystatin 100,000 U/mL, 4–6 mL 4 times daily OR 1–2 nystatin pastilles (200,000 U each) 4 times daily for 7–14 days.<br>Moderate-severe disease: fluconazole 6 mg/kg qd PO for 7–14 days (AII).<br>Esophageal: oral fluconazole (6–12 mg/kg/day, after a loading dose of 25 mg/kg/day) for 14–21 days. If cannot tolerate oral therapy, use fluconazole IV OR ABLC/L-AmB/AmB-D OR an echinocandin. | For fluconazole-refractory disease: itraconazole OR posaconazole OR AmB IV OR an echinocandin for 14–28 days.<br>Esophageal disease always requires systemic antifungal therapy.<br>Suppressive therapy (3 times weekly) with fluconazole is recommended for recurrent infections. |
| – Neonatal candidiasis[42] | AmB-D (1 mg/kg/day) is recommended therapy.<br>Fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day) is an alternative if patient has not been on fluconazole prophylaxis (BIII).[46] For treatment of neonates and young infants (<120 days) on ECMO, fluconazole is loaded with 35 mg/kg on day 1, followed by 12 mg/kg/day q24h (BII).<br>Lipid formulation AmB is an alternative but carries a theoretical risk of less urinary tract penetration compared with AmB-D.<br>Therapy is for 3 wk.<br>Echinocandins should be used with caution and generally limited to salvage therapy or to situations in which resistance or toxicity preclude the use of AmB-D or fluconazole. | In nurseries with high rates of candidiasis (>10%), IV or oral fluconazole prophylaxis (AI) (3–6 mg/kg twice weekly for 6 wk) in high-risk neonates (birth weight <1,000 g) is recommended. Oral nystatin, 100,000 units 3 times daily for 6 wk, is an alternative to fluconazole in neonates with birth weights <1,500 g in situations in which availability or resistance preclude the use of fluconazole<br>Lumbar puncture and thorough retinal examination recommended in neonates with cultures positive for *Candida* species from blood and/or urine (BIII).<br>CT or ultrasound imaging of genitourinary tract, liver, and spleen should be performed if blood cultures are persistently positive (BIII).<br>Assume meningoencephalitis in the neonate due to the high incidence of this complication. |

| | | |
|---|---|---|
| | | Role of flucytosine in neonates with meningitis is questionable and not routinely recommended due to toxicity concerns. The addition of flucytosine (100 mg/kg/day div q6h) may be considered as salvage therapy in patients who have not had a clinical response to initial AmB therapy, but adverse effects are frequent.<br>Central venous catheter removal is strongly recommended.<br>Infected CNS devices, including ventriculostomy drains and shunts, should be removed if possible. |
| – Chronic disseminated (hepatosplenic) candidiasis | Initial therapy with lipid formulation AmB (5 mg/kg daily) OR an echinocandin (caspofungin 70 mg/m$^2$ IV loading dose on day 1 [max dose 70 mg], followed by 50 mg/m$^2$ IV [max dose 70 mg] on subsequent days OR micafungin 2–4 mg/kg/day q24h [max dose 150 mg]) for several weeks, followed by oral fluconazole (12 mg/kg/day q24h, after a load of 25 mg/kg/day).<br>Therapy should continue until lesions resolve on repeat imaging, which is usually several months. Premature discontinuation of antifungal therapy can lead to relapse. | If chemotherapy or hematopoietic cell transplantation is required, it should not be delayed because of the presence of chronic disseminated candidiasis, and antifungal therapy should be continued throughout the period of high risk to prevent relapse. |
| – Peritonitis (secondary to peritoneal dialysis)[47,48] | Fluconazole 200 mg intraperitoneal q24h (AII) | Remove peritoneal dialysis catheter; replace after 4–6 wk of treatment, if possible.<br>High-dosage oral fluconazole may also be used.<br>AmB should not be instilled into the peritoneal cavity. |
| – Urinary tract infection | Cystitis: fluconazole 6 mg/kg qd IV or PO for 2 wk (AIII)<br>Pyelonephritis: fluconazole 12 mg/kg qd IV or PO for 2 wk (AII) after a loading dose of 25 mg/kg/day | Removing Foley catheter, if present, may lead to a spontaneous cure in the normal host; check for additional upper urinary tract disease.<br>For fluconazole-resistant organisms, AmB-D is an alternative.<br>AmB-D bladder irrigation is not generally recommended due to high relapse rate (an exception may be in fluconazole-resistant *Candida*). For renal collecting system fungus balls, surgical debridement may be required in non-neonates (BIII).<br>Echinocandins have poor urinary concentrations. |

**B. SYSTEMIC INFECTIONS** (continued)

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| – Vulvovaginal[49] | Topical vaginal cream/tablets/suppositories (alphabetic order): butoconazole, clotrimazole, econazole, fenticonazole, miconazole, sertaconazole, terconazole, or tioconazole for 3–7 days<br>OR fluconazole 10 mg/kg (max 150 mg) as a single dose (AII) | No topical agent is clearly superior.<br>Avoid azoles during pregnancy.<br>For recurring disease, consider 10–14 days of induction with topical or systemic azole followed by fluconazole once weekly for 6 mo. |
| – Cutaneous candidiasis | Topical therapy (alphabetic order): ciclopirox, clotrimazole, econazole, haloprogin, ketoconazole, miconazole, oxiconazole, sertaconazole, sulconazole | Fluconazole 6 mg/kg/day PO qd for 5–7 days |
| – Chronic mucocutaneous[39] | Fluconazole 6 mg/kg daily PO until lesions clear (AII) | Alternative: itraconazole 5 mg/kg PO solution q24h<br>Relapse common |
| **Chromoblastomycosis**[50–52] | Itraconazole oral solution 10 mg/kg/day div bid PO for 12–18 mo, in combination with surgical excision or repeated cryotherapy (AIII) | Alternative: terbinafine or an AmB |
| **Coccidioidomycosis**[53–59] | For moderate infections: fluconazole 12 mg/kg IV PO q24h (AII) after loading dose of 25 mg/kg/day.<br>For severe pulmonary disease: AmB-D 1 mg/kg/day IV q24h OR ABLC/L-AmB 5 mg/kg/day IV q24h (AIII) as initial therapy until clear improvement, followed by an oral azole for total therapy of up to 12 mo, depending on genetic or immunocompromised risk factors.<br>For meningitis: fluconazole 12 mg/kg/day IV q24h (AII) after loading dose of 25 mg/kg/day; for failures, intrathecal AmB-D (0.1–1.5 mg/dose) OR voriconazole IV (AIII). Lifelong azole suppressive therapy may be required. | Mild pulmonary disease does not require therapy in the normal host and only requires periodic reassessment.<br>Posaconazole also active, but little experience in children.<br>Treat until serum cocci complement fixation titers drop to 1:8 or 1:4, about 3–6 mo.<br>Disease in immunocompromised hosts may need to be treated longer, including potentially lifelong azole secondary prophylaxis.<br>Watch for relapse up to 1–2 y after therapy. |

| | | |
|---|---|---|
| | For extrapulmonary (non-meningeal), particularly for osteomyelitis: itraconazole solution 10 mg/kg/day div bid for 12 mo appears more effective than fluconazole (AIII), and AmB as an alternative if worsening. | |
| **Cryptococcosis**[60–64] | For mild-moderate pulmonary disease: fluconazole 12 mg/kg/day IV PO q24h after loading dose of 25 mg/kg/day for 6–12 mo (AII).<br>For meningitis or severe pulmonary disease: induction therapy with AmB-D 1–1.5 mg/kg/day IV q24h OR ABLC/L-AmB 5 mg/kg/day q24h; AND flucytosine 100 mg/kg/day PO div q6h for a minimum of 2 wk until CSF cleared, followed by consolidation therapy with fluconazole (12 mg/kg/day after a loading dose of 25 mg/kg/day) for a minimum of 8 more wk (AI). | Serum flucytosine concentrations should be obtained after 3-5 days to achieve a 2-h post-dose peak <100 µg/mL (and ideally 30–80 µg/mL) to prevent neutropenia.<br>For HIV-positive patients, continue maintenance therapy with fluconazole (6 mg/kg/day) indefinitely.<br>In organ transplant recipients, continue maintenance fluconazole (6 mg/kg/day) for 6–12 mo after consolidation therapy.<br>For cryptococcal relapse, restart induction therapy and determine antifungal susceptibility of relapse isolate. |
| ***Fusarium, Scedosporium prolificans, Pseudallescheria boydii*** (and its asexual form, ***Scedosporium apiospermum***),[28,65–69] and other agents of **hyalohyphomycosis** | Voriconazole 18 mg/kg/day IV div q12h for a loading dose on the first day, then 16 mg/kg/day IV div q12h as a maintenance dose for children 2–12 y. In children >12 y, use adult dosing (load 12 mg/kg/day IV div q12h on first day, then 8 mg/kg/day div q12h as a maintenance dose) (AII).<br>When stable, may switch from voriconazole IV to voriconazole PO at a dose of 18 mg/kg/day div bid for children 2–12 y and at least 400 mg/day div bid for children >12 y (AIII). | Optimal voriconazole trough concentrations (generally thought to be >2 µg/mL) are important.<br>Resistant to AmB in vitro.<br>Alternatives: echinocandins have been successful at salvage therapy in combination anecdotally; posaconazole (trough concentrations >0.7 µg/mL) likely helpful; while there are reports of combinations with terbinafine, terbinafine does not obtain good tissue concentrations for these disseminated infections.<br>These can be highly resistant infections, so strongly recommend antifungal susceptibility testing and consultation with a pediatric infectious diseases expert. |

**B. SYSTEMIC INFECTIONS** (continued)

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| **Histoplasmosis**[70–72] | For severe pulmonary disease: AmB-D 1 mg/kg/day q24h OR ABLC/L-AmB 5 mg/kg/day q24h for 1–2 wk, followed by itraconazole 10 mg/kg/day div bid to complete a total of 12 wk (AIII).<br>For mild-moderate acute pulmonary disease, itraconazole 10 mg/kg/day PO solution div bid for 6–12 wk (AIII). | Mild disease may not require therapy and, in most cases, resolves in 1 mo.<br>For disease with respiratory distress, ADD corticosteroids in first 1–2 wk of antifungal therapy.<br>Progressive disseminated or CNS disease requires AmB therapy for the initial 4–6 wk.<br>Potential lifelong suppressive itraconazole if cannot reverse immunosuppression. |
| **Mucormycosis** (previously known as zygomycosis)[73–77] | Requires aggressive surgery combined with induction antifungal therapy: L-AmB at 5–7.5 mg/kg/day q24h (AIII). ABLC should not be used at >5 mg/kg/day. Unclear if doses of L-AmB >5 mg/kg/day are helpful. Lipid formulations of AmB are preferred to AmB-D due to increased penetration and decreased toxicity.<br>Many experts advocate induction combination therapy with L-AmB plus an echinocandin.<br>Following successful induction antifungal therapy (for at least 3 wk), can continue consolidation therapy with posaconazole (or use intermittent L-AmB).<br>For salvage therapy, L-AmB at higher doses (10 mg/kg/day) or posaconazole (AIII) or isavuconazole. | Following clinical response with AmB, long-term oral step-down therapy with posaconazole (trough concentrations >0.7 μg/mL) can be attempted for 2–6 mo.<br>Isavuconazole with activity, but L-AmB preferred for initial therapy.<br>Voriconazole has NO activity against mucormycosis or other *Zygomycetes*.<br>Return of immune function is paramount to treatment success; for children receiving corticosteroids, decreasing the corticosteroid dosage or changing to steroid-sparing protocols is also important. |
| **Paracoccidioidomycosis**[78–81] | Itraconazole 10 mg/kg/day PO solution div bid for 6 mo (AIII) OR ketoconazole 5 mg/kg/day PO q24h for 6 mo (BIII) | Alternatives: voriconazole; sulfadiazine or TMP/SMX for 3–5 y.<br>AmB is another alternative and may be combined with sulfa or azole antifungals. |

| | | |
|---|---|---|
| ***Pneumocystis jiroveci* (*carinii*) pneumonia**[82,83] | Severe disease: preferred regimen is TMP/SMX 15–20 mg TMP component/kg/day IV div q8h (AI) OR, for TMP/SMX intolerant or TMP/SMX treatment failure, pentamidine isethionate 4 mg base/kg/day IV daily (BII), for 3 wk.<br>Mild-moderate disease: start with IV therapy, then after acute pneumonitis is resolved, TMP/SMX 20 mg TMP component/kg/day PO div qid for 3 wk total treatment course (AII). | Alternatives: TMP AND dapsone; OR primaquine AND clindamycin; OR atovaquone.<br>Prophylaxis: preferred regimen is TMP/SMX (5 mg TMP component/kg/day) PO div bid 3 times/wk on consecutive days; OR same dose, given qd, every day; OR atovaquone: 30 mg/kg/day for infants 1–3 mo; 45 mg/kg/day for infants/children 4–24 mo; and 30 mg/kg/day for children >24 mo; OR dapsone 2 mg/kg (max 100 mg) PO qd, OR dapsone 4 mg/kg (max 200 mg) PO once weekly.<br>Use steroid therapy for more severe disease. |
| **Sporotrichosis**[84,85] | For cutaneous/lymphocutaneous: itraconazole 10 mg/kg/day div bid PO solution for 2–4 wk after all lesions gone (generally total of 3–6 mo) (AII).<br>For serious pulmonary or disseminated infection or disseminated sporotrichosis: ABLC/L-AmB at 5 mg/kg/day q24h until stable, then step-down therapy with itraconazole PO for a total of 12 mo (AIII).<br>For less severe disease, itraconazole for 12 mo. | If no response for cutaneous disease, treat with higher itraconazole dose, terbinafine, or saturated solution of potassium iodide. Fluconazole is less effective.<br>Obtain serum concentrations of itraconazole after 2 wk of therapy; want serum trough concentration >0.5 µg/mL.<br>For meningeal disease, initial AmB should be 4–6 wk before change to itraconazole for at least 12 mo of therapy.<br>Surgery may be necessary in osteoarticular or pulmonary disease. |

## C. LOCALIZED MUCOCUTANEOUS INFECTIONS

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| **Dermatophytoses** | | |
| – Scalp (tinea capitis, including kerion)[86–90] | Griseofulvin ultramicrosized 10–15 mg/kg/day or microsized 20–25 mg/kg/day qd PO for 2 mo or longer (AII) (taken with milk or fatty foods to augment absorption).<br>For kerion, treat concurrently with prednisone (1–2 mg/kg/day for 1–2 wk) (AIII).<br>Terbinafine can be considered the optimal choice for *Trichophyton* infections and used for only 2–4 weeks. Terbinafine dosing is 62.5 mg/day (<20 kg), 125 mg/day (20–40 kg), or 250 mg/day (>40 kg). | No need to routinely follow liver function tests in normal healthy children taking griseofulvin.<br>2.5% selenium sulfide shampoo, or 2% ketoconazole shampoo, 2–3 times/wk should be used concurrently to prevent recurrences.<br>Alternatives: itraconazole solution 5 mg/kg PO qd, or fluconazole PO; terbinafine superior for *Trichophyton* spp, but griseofulvin superior for *Microsporum* spp. |
| – Tinea corporis (infection of trunk/limbs/face)<br>– Tinea cruris (infection of the groin)<br>– Tinea pedis (infection of the toes/feet) | Alphabetic order of topical agents: butenafine, ciclopirox, clotrimazole, econazole, haloprogin, ketoconazole, miconazole, naftifine, oxiconazole, sertaconazole, sulconazole, terbinafine, and tolnaftate (AII); apply daily for 4 wk. | For unresponsive tinea lesions, use griseofulvin PO in dosages provided above; fluconazole PO; itraconazole PO; OR terbinafine PO.<br>For tinea pedis: Terbinafine PO or itraconazole PO are preferred over other oral agents.<br>Keep skin as clean and dry as possible, particularly for tinea cruris and tinea pedis. |
| – Tinea unguium (onychomycosis)[88,91,92] | Terbinafine 62.5 mg/day (<20 kg), 125 mg/day (20–40 kg), or 250 mg/day (>40 kg). Use for at least 6 weeks (fingernails) or at least 12 weeks (toenails). | Recurrence or partial response common.<br>Alternative: Itraconazole pulse therapy with 5 mg/kg PO per day for 1 wk per mo. Two pulses for fingernails and 3 pulses for toenails.<br>Alternatives: fluconazole, griseofulvin. |
| – Tinea versicolor (also pityriasis versicolor)[88,93,94] | Apply topically: selenium sulfide 2.5% lotion or 1% shampoo daily, leave on 30 min, then rinse; for 7 d, then monthly for 6 mo (AIII); OR ciclopirox 1% cream for 4 wk (BII); OR terbinafine 1% solution (BII); OR ketoconazole 2% shampoo daily for 5 days (BII)<br>For small lesions, topical clotrimazole, econazole, haloprogin, ketoconazole, miconazole, or naftifine | For lesions that fail to clear with topical therapy or for extensive lesions: fluconazole PO or itraconazole PO are equally effective.<br>Recurrence common. |

## 9. Preferred Therapy for Specific Viral Pathogens

### NOTE

- **Abbreviations:** AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; ARV, antiretroviral; bid, twice daily; BSA, body surface area; CDC, Centers for Disease Control and Prevention; CLD, chronic lung disease; CMV, cytomegalovirus; CrCl, creatinine clearance; div, divided; EBV, Epstein-Barr virus; FDA, US Food and Drug Administration; G-CSF, granulocyte-colony stimulating factor; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HHS, US Department of Health and Human Services; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IFN, interferon; IG, immune globulin; IM, intramuscular; IV, intravenous; NRTI, nucleoside analog reverse transcriptase inhibitor; PO, orally; postmenstrual age, weeks of gestation since last menstrual period PLUS weeks of chronologic age since birth; PTLD, posttransplant lymphoproliferative disorder; qd, once daily; qid, 4 times daily; RSV, respiratory syncytial virus; SQ, subcutaneous; tid, 3 times daily; WHO, World Health Organization.

## A. OVERVIEW OF NON-HIV VIRAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIVIRALS

| Virus | Acyclovir | Adefovir | Cidofovir | Entecavir | Famciclovir | Foscarnet | Ganciclovir |
|---|---|---|---|---|---|---|---|
| Cytomegalovirus | | | + | | | + | ++ |
| Hepatitis B virus | | + | | ++ | | | |
| Hepatitis C virus | | | | | | | |
| Herpes simplex virus | ++ | | | | ++ | + | + |
| Influenza A and B | | | | | | | |
| Varicella-zoster virus | ++ | | | | ++ | + | + |

| Virus | Interferon alfa-2b | Lamivudine | Ombitasvir/Paritaprevir/ Ritonavir Copackaged With Dasabuvir (ViekiraPak) | Oseltamivir | Pegylated Interferon alfa-2a | Peramivir | Ribavirin |
|---|---|---|---|---|---|---|---|
| Cytomegalovirus | | | | | | | |
| Hepatitis B virus | + | + | | | ++ | | |
| Hepatitis C virus | | | ++ | | ++ | | ++ |
| Herpes simplex virus | | | | | | | |
| Influenza A and B | | | | ++ | | + | |
| Varicella-zoster virus | | | | | | | |

| Virus | Simeprevir | Sofosbuvir/ Ledipasvir (Harvoni) | Telbivudine | Tenofovir | Valacyclovir | Valganciclovir | Zanamivir |
|---|---|---|---|---|---|---|---|
| Cytomegalovirus | | | | | | ++ | |
| Hepatitis B virus | | | + | ++ | | | |
| Hepatitis C virus | ++ | ++ | | | | | |
| Herpes simplex virus | | | | | ++ | + | |
| Influenza A and B | | | | | | | + |
| Varicella-zoster virus | | | | | ++ | | |

NOTE: ++ = preferred therapy(ies); + = acceptable therapy.

## B. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| **Adenovirus** (pneumonia or disseminated infection in immunocompromised hosts)[1] | Cidofovir and ribavirin are active in vitro, but no prospective clinical data exist and both have significant toxicity.<br>Two cidofovir dosing schedules have been employed in clinical settings: (1) 5 mg/kg/dose IV once weekly or (2) 1–1.5 mg/kg/dose IV 3 times/wk. If parenteral cidofovir is utilized, IV hydration and oral probenecid should be used to reduce renal toxicity. | Brincidofovir, the orally bioavailable lipophilic derivative of cidofovir also known as CMX001, is under investigation for the treatment of adenovirus in immunocompromised hosts. It is not yet commercially available. |
| **Cytomegalovirus** | | |
| – Neonatal[2] | See Chapter 5. | |
| – Immunocompromised (HIV, chemotherapy, transplant-related)[3–15] | For induction: ganciclovir 10 mg/kg/day IV div q12h for 14–21 days (AII) (may be increased to 15 mg/kg/day IV div q12h).<br>For maintenance: 5 mg/kg IV q24h for 5–7 days per week. Duration dependent on degree of immunosuppression (AII).<br>CMV hyperimmune globulin may decrease morbidity in bone marrow transplant patients with CMV pneumonia (AII). | Use foscarnet or cidofovir for ganciclovir-resistant strains; for HIV-positive children on HAART, CMV may resolve without therapy.<br>Also used for prevention of CMV disease posttransplant for 100–120 days.<br>Data on valganciclovir dosing in young children for treatment of retinitis are unavailable, but consideration can be given to transitioning from IV ganciclovir to oral valganciclovir after improvement of retinitis is noted. Limited data on oral valganciclovir in infants[16,17] (32 mg/kg/day PO div bid) and children [dosing by BSA (dose [mg] = 7 × BSA × CrCl)].[5] |
| – Prophylaxis of infection in immunocompromised hosts[4,18] | Ganciclovir 5 mg/kg IV daily (or 3 times/wk) (started at engraftment for stem cell transplant patients) (BII)<br>Valganciclovir at total dose in milligrams = 7 × BSA × CrCl (use maximum CrCl 150 mL/min/1.73 $m^2$) orally once daily with food for | Neutropenia is a complication with ganciclovir prophylaxis and may be addressed with G-CSF.<br>Prophylaxis and preemptive strategies are effective; neither has been shown clearly superior to the other.[9] |

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|---|---|---|
| | children 4 mo–16 y (max dose 900 mg/day) for primary prophylaxis in HIV patients[19] who are CMV antibody positive and have severe immunosuppression (CD4 count <50 cells/mm$^3$ in children ≥6 y; CD4 percentage <5% in children <6 y) (CIII) | |
| **Epstein-Barr virus** | | |
| – Mononucleosis, encephalitis[20–22] | Limited data suggest small clinical benefit of valacyclovir in adolescents for mononucleosis (3 g/day div tid for 14 days) (CIII).<br>For EBV encephalitis: ganciclovir IV OR acyclovir IV (AIII). | No prospective data on benefits of acyclovir IV or ganciclovir IV in EBV clinical infections of normal hosts.<br>Patients suspected to have infectious mononucleosis should not be given ampicillin or amoxicillin, which cause nonallergic morbilliform rashes in a high proportion of patients with active EBV infection (AII).<br>Therapy with short-course corticosteroids (prednisone 1 mg/kg per day PO [maximum 20 mg/day] for 7 days with subsequent tapering) may have a beneficial effect on acute symptoms in patients with marked tonsillar inflammation with impending airway obstruction, massive splenomegaly, myocarditis, hemolytic anemia, or hemophagocytic lymphohistiocytosis (BIII). |
| – Posttransplant lymphoproliferative disorder[23,24] | Ganciclovir (AIII) | Decrease immune suppression if possible, as this has the most impact on control of EBV; rituximab, methotrexate have been used but without controlled data.<br>Preemptive treatment with ganciclovir may decrease PTLD in solid organ transplants. |

## B. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| **Hepatitis B virus** (chronic)[25–38] | IFN-alpha 3 million U/m² BSA SQ 3 times/wk for 1 wk, followed by dose escalation to 6 million U/m² BSA (max 10 million U/dose), to complete a 24-wk course for children 1–18 y; OR lamivudine 3 mg/kg/day (max 100 mg) PO q24h for 52 wk for children ≥2 y (children coinfected with HIV and HBV should use the approved dose for HIV) (AII); OR adefovir for children ≥12 y (10 mg PO q24h for a minimum of 12 mo; optimum duration of therapy unknown) (BII); OR entecavir for children ≥16 y (0.5 mg qd in patients who have not received prior nucleoside therapy; 1 mg qd in patients who are previously treated [not first choice in this setting]); optimum duration of therapy unknown (BII) | Indications for treatment of chronic HBV infection, with or without HIV coinfection, are: (1) evidence of ongoing HBV viral replication, as indicated by serum HBV DNA (>20,000 without HBeAg positivity or >2,000 IU/mL with HBeAg positivity) for >6 mo and persistent elevation of serum transaminase levels for >6 mo, or (2) evidence of chronic hepatitis on liver biopsy (BII). Antiviral therapy is not warranted in children without necroinflammatory liver disease (BIII). Treatment is not recommended for children with immunotolerant chronic HBV infection (ie, normal serum transaminase levels despite detectable HBV DNA) (BII).<br>Standard IFN-alfa (IFN-2a or -2b) is recommended for treating chronic HBV infection with compensated liver disease in HIV-uninfected children aged ≥2 y who warrant treatment (AI). IFN-alfa therapy in combination with oral antiviral therapy cannot be recommended for pediatric HBV infection in HIV-uninfected children until more data are available (BII).<br>In HIV/HBV-coinfected children who do not require ART for their HIV infection, IFN-alpha therapy is the preferred agent to treat chronic HBV (BIII), whereas adefovir can be considered in children ≥12 y (BIII). Treatment options for HIV/HBV-coinfected children who meet criteria for HBV therapy and who are already receiving lamivudine- or emtricitabine-containing HIV-suppressive ART, include the standard IFN-alpha therapy to the ARV regimen (BIII), or adefovir if the child can receive adult dosing (BIII), or use of tenofovir disoproxil fumarate in lamivudine (or emtricitabine)-containing ARV regimen in children ≥2 y (BIII). HIV/HBV-coinfected children should not be given |

lamivudine (or emtricitabine) without additional anti-HIV drugs for treatment of chronic HBV (CIII).[19]

Alternatives

Tenofovir (adult and adolescent dose [≥12 y] 300 mg qd).

Telbivudine (adult dose 600 mg qd). There are not sufficient clinical data to identify the appropriate dose for use in children.

Lamivudine approved for children ≥2 y, but antiviral resistance develops on therapy in 30%.

Entecavir is superior to lamivudine in the treatment of chronic HBV infection and is the most potent anti-HBV agent available.

## B. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| **Hepatitis C virus** (chronic)[39–45] | Treatment of HCV infections in adults has been revolutionized over the past 2 years with the licensure of numerous highly effective direct-acting antiviral drugs for use in adults. Studies of many of these drugs are beginning soon in children. Given the efficacy of these new treatment regimens in adults (AI),[46–61] strong consideration should be given to seeking out these studies if treatment is desired in children and adolescents. An alternative would be to not treat with the approved treatment regimen of IFN + ribavirin pending results of these pediatric studies.<br>If treatment currently is desired and access to the studies of direct-acting antiviral agents is not available, the following treatment is the only one FDA approved for HCV infection in children 3–17 y:<br>Pegylated IFN-alpha: 2a 180 µg/1.73 $m^2$ BSA SQ once per wk (maximum dose 180 µg) OR 2b 60 µg/$m^2$ BSA once per wk<br>PLUS<br>Ribavirin (oral) 7.5 mg/kg body weight twice daily (fixed dose by weight recommended)<br>25–36 kg: 200 mg in am and pm<br>>36–49 kg: 200 mg in am and 400 mg in pm<br>>49–61 kg: 400 mg in am and pm<br>>61–75 kg: 400 mg in am and 600 mg in pm<br>>75 kg: 600 mg in am and pm<br>Treatment duration: 24–48 wk (AII) | Since 2010, 8 antiviral drugs have been licensed for use in the US: boceprevir (2011), dasabuvir (2014), ledipasvir (2014), ombitasvir (2014), paritaprevir (2014), simeprevir (2013), sofosbuvir (2014), and telaprevir (2011). Many of the most promising hepatitis C drugs are used in fixed combinations (sofosbuvir plus ledipasvir, under the brand name Harvoni; ombitasvir, paritaprevir, and ritonavir copackaged with dasabuvir, under the brand name ViekiraPak). None currently have been approved for use in children. This pace of development of hepatitis C antivirals has been so rapid as to make some of the first-generation products (boceprevir, telaprevir) obsolete already given the improved potency of the newer generation drugs.<br>Treatment of children <3 y who have HCV infection usually is not recommended (BIII).<br>HCV-infected, HIV-uninfected children ≥3 y should be individualized because HCV usually causes mild disease in this population and few data exist to identify risk factors differentiating those at greater risk for progression of liver disease. Those who are chosen for treatment should receive combination therapy with IFN-alpha and ribavirin for 48 wk for genotype 1 and 24 wk for genotypes 2 or 3 (AI) (see Therapy column, left).<br>Treatment should be considered for all HIV/HCV-coinfected children aged >3 y who have no contraindications to treatment (BIII).<br>A liver biopsy to stage disease is recommended before deciding whether to initiate therapy for chronic HCV genotype 1 infection (BIII). However, some specialists would treat children infected with HCV genotypes 2 or 3 without first obtaining a liver biopsy (BIII). |

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|---|---|---|
| | | IFN-alpha therapy is contraindicated for children with decompensated liver disease, substantial cytopenias, renal failure, severe cardiac or neuropsychiatric disorders, and non–HCV-related autoimmune disease (AII).[19] |
| **Herpes simplex virus** | | |
| – Third trimester maternal suppressive therapy[62,63] | Acyclovir or valacyclovir maternal suppressive therapy in pregnant women reduces HSV recurrences and viral shedding at the time of delivery but does not fully prevent neonatal HSV[64] (BIII). | |
| – Neonatal | See Chapter 5. | |
| – Mucocutaneous (normal host) | Acyclovir 80 mg/kg/day PO div qid (max dose: 800 mg) for 5–7 days, or 15 mg/kg/day IV as 1–2 h infusion div q8h (AII)<br>Suppressive therapy for frequent recurrence (no pediatric data): 20 mg/kg/dose given bid or tid (max dose: 400 mg) for 6–12 mo, then reevaluate need (AIII)<br>Valacyclovir 20 mg/kg/dose (max dose: 1 g) PO bid[65] for 5–7 days (BII) | Foscarnet for acyclovir-resistant strains.<br>Immunocompromised hosts may require 10–14 days of therapy.<br>Topical acyclovir not efficacious and therefore is not recommended. |
| – Genital | Adult doses: acyclovir 400 mg PO tid, for 7–10 days; OR valacyclovir 1 g PO bid for 10 days; OR famciclovir 250 mg PO tid for 7–10 days (AI) | All 3 drugs have been used as prophylaxis to prevent recurrence.<br>Topical acyclovir not efficacious and therefore is not recommended. |
| – Encephalitis | Acyclovir 60 mg/kg/day IV as 1–2 h infusion div q8h; for 21 days for infants ≤4 mo. For older infants and children, 45–60 mg/kg/day IV (AIII). | Safety of high-dose acyclovir (60 mg/kg/day) not well defined beyond the neonatal period; can be used but monitor for neurotoxicity and nephrotoxicity. |
| – Keratoconjunctivitis | 1% trifluridine or 0.15% ganciclovir ophthalmic gel (AII) | Treat in consultation with an ophthalmologist.<br>Topical steroids may be helpful when used together with antiviral agents. |

## B. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| **Human herpesvirus 6** | | |
| – Immunocompromised children[66] | No prospective comparative data; ganciclovir 10 mg/kg/day IV div q12h used in case report (AIII) | May require high dose to control infection; safety and efficacy not defined at high doses. |
| **Human immunodeficiency virus** | | |
| Current information on HIV treatment and opportunistic infections for children[67] is posted at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf (accessed August 31, 2015); other information on HIV programs is available at www.cdc.gov/hiv/policies/index.html (accessed August 31, 2015). Consult with an HIV expert, if possible, for current recommendations, as treatment options are complicated and constantly evolving. | | |
| **– Therapy of HIV infection** State-of-the-art therapy is rapidly evolving with introduction of new agents and combinations; currently there are 23 individual ARV agents approved for use by the FDA that have pediatric indications, as well as multiple combinations; guidelines for children and adolescents are continually updated on the AIDSinfo and CDC Web sites given previously. | Effective therapy (HAART) consists of ≥3 agents, including 2 nucleoside reverse transcriptase inhibitors, plus a protease inhibitor or non-nucleoside reverse transcriptase inhibitor (integrase inhibitors are currently available for 2nd-line therapy options); many different combination regimens give similar treatment outcomes; choice of agents depends on the age of the child, viral load, consideration of potential viral resistance, and extent of immune depletion, in addition to judging the child's ability to adhere to the regimen. | Assess drug toxicity (based on the agents used) and virologic/immunologic response to therapy (quantitative plasma HIV and CD4 count) initially monthly and then every 3–6 mo during the maintenance phase. |
| – Children of any age | Any child with AIDS or significant HIV-related symptoms (clinical category C and most B conditions) should be treated (AI).<br>New guidance from the WHO and HHS guidelines committees now recommend treatment for all children regardless of age, CD4 count, or clinical status, with situation-specific levels of urgency. | Adherence counseling and appropriate ARV formulations are critical for successful implementation. |

| | | |
|---|---|---|
| – First year of life | HAART with ≥3 drugs is now recommended for all infants ≤12 mo, regardless of clinical status or laboratory values (AI for <12 wk; AII for 12–52 wk). | Preferred therapy in the first year of life is zidovudine plus lamivudine plus lopinavir/ritonavir (toxicity concerns preclude its use until a postmenstrual age of 42 wk and a postnatal age of at least 14 days is reached). |
| – HIV-infected children ≥1 y who are asymptomatic or have mild symptoms | Treat all with evidence grade for the following CD4 values:<br>Age 1–<6 y with CD4 <1,000 or <25% (AII)<br>Age 1–<6 y with CD4 ≥1,000 or ≥25% (BI)<br>Age ≥6 y with CD4 <500 (AII)<br>Age ≥6 y with CD4 ≥500 (BI) | Preferred regimens comprise zidovudine plus lamivudine (at any age) OR abacavir plus lamivudine (>3 mo) OR tenofovir plus emtricitabine (aka Truvada) (adolescents/Tanner stage 4 or 5) PLUS lopinavir/ritonavir (any age >2 wk) OR efavirenz (≥3 y) OR atazanavir/ritonavir (≥6 y). |
| – Antiretroviral-experienced child | Consult with HIV specialist. | Consider treatment history and drug resistance testing and assess adherence. |
| **– HIV exposures, nonoccupational** | Therapy recommendations for exposures available on the CDC Web site at www.cdc.gov/hiv/guidelines/preventing.html (last updated 2005) (accessed August 31, 2015) and at New York State Department of Health AIDS Institute. UPDATE: HIV prophylaxis following nonoccupational exposure. July 2013. www.hivguidelines.org/clinical-guidelines/post-exposure-prophylaxis/hiv-prophylaxis-following-non-occupational-exposure (accessed October 26, 2015), based on assessment of risk of HIV exposure. | Postexposure prophylaxis remains unproven; consider individually regarding risk, time from exposure, and likelihood of adherence; prophylactic regimens administered for 4 wk. |
| – Negligible exposure risk (urine, nasal secretions, saliva, sweat, or tears—no visible blood in secretions) OR >72 h since exposure | Prophylaxis not recommended (BIII) | |

## B. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| – Significant exposure risk (blood, semen, vaginal, or rectal secretions from a known HIV-infected individual) AND <72 h since exposure | Prophylaxis recommended (BIII): Combivir (zidovudine/lamivudine) or Truvada (tenofovir/emtricitabine) PLUS efavirenz or Kaletra (lopinavir/ritonavir).<br>Since the last HHS/CDC guidelines in 2005, raltegravir or darunavir/ritonavir in place of efavirenz or lopinavir/ritonavir has gained favor among experts. | Preferred prophylactic regimens<br>– Based on treatment regimens for infected individuals<br>– 28-day regimen<br>In the event of poor adherence or toxicity, some experts consider 2 NRTI regimens, such as Combivir (zidovudine/lamivudine) or Truvada (tenofovir/emtricitabine) (BIII). |
| – HIV exposure, occupational[68] | See guidelines on CDC Web site at www.cdc.gov/hiv/guidelines/preventing.html (accessed August 31, 2015). | |
| **Influenza virus**<br>Recommendations for the treatment of influenza can vary from season to season; access the American Academy of Pediatrics Web site (www.aap.org) and the CDC Web site (www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm, accessed August 31, 2015) for the most current, accurate information. | | |
| **Influenza A and B** | | |
| – Treatment[69–71] | Oseltamivir<br>Preterm, <38 wk postmenstrual age: 1 mg/kg/dose PO bid[69]<br>Preterm, 38–40 wk postmenstrual age: 1.5 mg/kg/dose PO bid[69]<br>Preterm, >40 wk postmenstrual age: 3.0 mg/kg/dose PO bid<br>Term, birth–8 mo: 3.0 mg/kg/dose PO bid<br>9–11 mo: 3.5 mg/kg/dose PO bid[70]<br>12–23 mo: 30 mg/dose PO bid<br>2–12 y: ≤15 kg: 30 mg bid; 16–23 kg: 45 mg bid; 24–40 kg: 60 mg bid; >40 kg: 75 mg bid | Oseltamivir currently is drug of choice for treatment of influenza infections.<br>For patients 12–23 mo, the original FDA-approved unit dose of 30 mg/dose may provide inadequate drug exposure; 3.5 mg/kg/dose PO bid has been studied,[70] but study population sizes were small.<br>Peramivir is a third neuraminidase inhibitor that was approved for use in adults in the US in December 2014. Pediatric studies are underway.<br>The adamantanes, amantadine and rimantadine, currently are not effective for treatment due to near-universal resistance of influenza A. |

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| | ≥13 y: 75 mg bid OR zanamivir<br>≥7 y: 10 mg by inhalation bid for 5 days | |
| – Chemoprophylaxis | Oseltamivir<br>3 mo–12 y: The prophylaxis dose is one-half of the treatment does for all ages; the same mg dose that is given twice daily for treatment is given once daily for prophylaxis.<br>Zanamivir<br>≥5 y: 10 mg by inhalation qd for as long as 28 days (community outbreaks) or 10 days (household setting) | Oseltamivir currently is drug of choice for chemoprophylaxis of influenza infection.<br>Unless the situation is judged critical, oseltamivir chemoprophylaxis not recommended for patients <3 mo because of limited safety and efficacy data in this age group.<br>The adamantanes, amantadine and rimantadine, currently are not effective for chemoprophylaxis due to near-universal resistance of influenza A. |
| **Measles**[72] | No prospective data on antiviral therapy. Ribavirin is active against measles virus in vitro.<br>Vitamin A is beneficial in children with measles and is recommended by the World Health Organization for all children with measles regardless of their country of residence (qd dosing for 2 days): for children ≥1 y: 200,000 IU; for infants 6–12 mo: 100,000 IU; for infants <6 mo: 50,000 IU (BII). Even in countries where measles is not usually severe, vitamin A should be given to all children with severe measles (eg, requiring hospitalization). Parenteral and oral formulations are available in the US. | IG prophylaxis for exposed, susceptible children: 0.5 mL/kg (max 15 mL) IM |
| **Respiratory syncytial virus**[73,74] | | |
| – Therapy (severe disease in compromised host) | Ribavirin (6-g vial to make 20 mg/mL solution in sterile water), aerosolized over 18–20 h daily for 3–5 days (BII) | Aerosol ribavirin provides a small benefit and should only be used for life-threatening infection with RSV. Airway reactivity with inhalation precludes routine use. |

## B. PREFERRED THERAPY FOR SPECIFIC VIRAL PATHOGENS (continued)

| Infection | Therapy (evidence grade) | Comments |
|---|---|---|
| – Prophylaxis (palivizumab, Synagis for high-risk infants) (BI)[73,74] | Prophylaxis: palivizumab (a monoclonal antibody) 15 mg/kg IM monthly (maximum: 5 doses) for the following high-risk infants (AI):<br>In first y of life, palivizumab prophylaxis is recommended for infants born before 29 wk, 0 days' gestation.<br>Palivizumab prophylaxis is not recommended for otherwise healthy infants born at ≥29 wk, 0 days' gestation.<br>In first y of life, palivizumab prophylaxis is recommended for preterm infants with CLD of prematurity, defined as birth at <32 wk, 0 days' gestation and a requirement for >21% oxygen for at least 28 days after birth.<br>Clinicians may administer palivizumab prophylaxis in the first year of life to certain infants with hemodynamically significant heart disease. | Palivizumab does not provide benefit in the treatment of an active RSV infection.<br>Palivizumab prophylaxis may be considered for children <24 mo who will be profoundly immunocompromised during the RSV season.<br>Palivizumab prophylaxis is not recommended in the second year of life except for children who required at least 28 days of supplemental oxygen after birth and who continue to require medical support (supplemental oxygen, chronic corticosteroid therapy, or diuretic therapy) during the 6-mo period before the start of the second RSV season.<br>Monthly prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.<br>Children with pulmonary abnormality or neuromuscular disease that impairs the ability to clear secretions from the upper airways may be considered for prophylaxis in the first year of life.<br>Insufficient data are available to recommend palivizumab prophylaxis for children with cystic fibrosis or Down syndrome.<br>The burden of RSV disease and costs associated with transport from remote locations may result in a broader use of palivizumab for RSV prevention in Alaska Native populations and possibly in selected other American Indian populations.<br>Palivizumab prophylaxis is not recommended for prevention of health care–associated RSV disease. |

| **Varicella-zoster virus**[75] | | |
|---|---|---|
| – Infection in a normal host | Acyclovir 80 mg/kg/day (max single dose 800 mg) PO div qid for 5 days (AI) | The sooner antiviral therapy can be started, the greater the clinical benefit. |
| – Severe primary chickenpox, disseminated infection (cutaneous, pneumonia, encephalitis, hepatitis); immunocompromised host with primary chickenpox or disseminated zoster | Acyclovir 30 mg/kg/day IV as 1–2 h infusion div q8h for 10 days (acyclovir doses of 45–60 mg/kg/day in 3 div doses IV should be used for disseminated or central nervous system infection). Dosing also can be provided as 1,500 mg/m$^2$/day IV div q8h. Duration in immunocompromised children: 7–14 days, based on clinical response (AI). | Oral valacyclovir, famciclovir, foscarnet also active |

## 10. Preferred Therapy for Specific Parasitic Pathogens

### NOTES

- For some parasitic diseases, therapy may be available only from the Centers for Disease Control and Prevention (CDC), as noted. The CDC provides up-to-date information about parasitic diseases and current treatment recommendations at www.cdc.gov/parasites. Consultation is available from the CDC for parasitic disease diagnostic services (www.cdc.gov/dpdx, accessed September 1, 2015), parasitic disease testing, and experimental therapy at 404/639-3670; for malaria, 770/488-7788 or 855/856-4713 Monday through Friday, 9:00 am to 5:00 pm ET, and 770/488-7100 after hours, weekends, and holidays. Antiparasitic drugs available from the CDC can be reviewed and requested at www.cdc.gov/laboratory/drugservice/formulary.html (accessed September 1, 2015).
- Additional information about many of the organisms and diseases mentioned here, along with treatment recommendations, can be found in the appropriate sections in the American Academy of Pediatrics *Red Book*.
- **Abbreviations:** AmB, amphotericin B; A-P, atovaquone/proguanil; bid, twice daily; BP, blood pressure; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CrCl, creatinine clearance; CSF, cerebrospinal fluid; DEC, diethylcarbamazine; div, divided; DS, double strength; ECG, electrocardiogram; FDA, US Food and Drug Administration; G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous; MRI, magnetic resonance imaging; PAIR, percutaneous aspiration, injection, re-aspiration; PHMB, polyhexamethylene biguanide; PO, orally; qd, once daily; qid, 4 times daily; qod, every other day; spp, species; tab, tablet; tid, 3 times daily; TMP/SMX, trimethoprim/sulfamethoxazole.

## PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS

| Disease/Organism | Treatment (evidence grade) | Comments |
|---|---|---|
| **AMEBIASIS**[1–5] | | |
| *Entamoeba histolytica* | | |
| – Asymptomatic intestinal colonization | Paromomycin 25–35 mg/kg/day PO div tid for 7 days; OR iodoquinol 30–40 mg/kg/day (max 650 mg/dose) PO div tid for 20 days; OR diloxanide furoate (not commercially available in the US) 20 mg/kg/day PO div tid (max 500 mg/dose) for 10 days (CII) | Follow-up stool examination to ensure eradication of carriage; screen/treat positive close contacts.<br>*Entamoeba dispar* infections do not require treatment.<br>Preliminary data supports use of nitazoxanide, age ≥12 y, 500 mg bid for 3 days; ages 4–11 y, 200 mg bid for 3 days; ages 1–3 y, 100 mg bid for 3 days. |
| – Colitis | Metronidazole 35–50 mg/kg/day PO div tid for 10 days; OR tinidazole (age >3 y) 50 mg/kg/day PO (max 2 g) qd for 3 days FOLLOWED by paromomycin or iodoquinol as above to eliminate cysts (BII) | Avoid anti-motility drugs, steroids.<br>Take tinidazole with food to decrease GI side effects; if unable to take tabs, pharmacists can crush tabs and mix with syrup.<br>Avoid alcohol ingestion with metronidazole and tinidazole.<br>Preliminary data to support use of nitazoxanide, age ≥12 y, 500 mg bid for 3 days; ages 4–11 y, 200 mg bid for 3 days; ages 1–3 y, 100 mg bid for 3 days. |
| – Liver abscess, extraintestinal disease | Metronidazole 35–50 mg/kg/day IV q8h, switch to PO when tolerated, for 10 days; OR tinidazole (age >3 y) 50 mg/kg/day PO (max 2 g) qd for 5 days FOLLOWED by paromomycin or iodoquinol as above to eliminate cysts (BII)<br>Nitazoxanide 500 mg bid for 10 days (≥12 y) | Serologic assays >95% positive in extraintestinal amebiasis.<br>Percutaneous or surgical drainage may be indicated for large liver abscesses or inadequate response to medical therapy.<br>Avoid alcohol ingestion with metronidazole and tinidazole.<br>Take tinidazole with food to decrease GI side effects; if unable to take tabs, pharmacists can crush tabs and mix with syrup. |

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| **MENINGOENCEPHALITIS**[6–10] | | |
| *Naegleria, Acanthamoeba, Balamuthia, Hartmannella* spp | *Naegleria:* AmB 1.5 mg/kg/day IV qd for 9–30 days ± intrathecally PLUS rifampin 10 mg/kg/day PO qd or div tid PLUS fluconazole 10 mg/kg/day IV or PO qd OR miconazole 350 mg/m$^2$/day IV div tid PLUS miltefosine (available from CDC) <45 kg 50 mg PO bid; ≥45 kg 50 mg PO tid PLUS azithromycin 500 mg IV or PO<br>*Acanthamoeba:* Treatment uncertain; combination regimens including miltefosine (available from CDC), fluconazole, and pentamidine favored by some experts; TMP/SMX, metronidazole, and a macrolide may be added. Other drugs that have been used alone or in combination include rifampin, azoles, pentamidine, sulfadiazine, flucytosine, and caspofungin.<br>Keratitis: Topical therapies include biguanide chlorhexidine or PHMB (0.02%), combined with propamidine isethionate (0.1%) or hexamidine (0.1%) (topical therapies not approved in US but available at compounding pharmacies).<br>*Balamuthia:* Treatment uncertain; combination regimens preferred. Drugs that have been used alone or in combination include pentamidine, 5-flucytosine, fluconazole, macrolides, sulfadiazine, miltefosine (available from CDC), thioridazine, AmB, itraconazole, and albendazole. | Liposomal AmB is less effective in animal models.<br>Treatment outcomes usually unsuccessful; early therapy (even before diagnostic confirmation if indicated) may improve survival.<br>Keratitis should be evaluated by an ophthalmologist.<br>Prolonged treatment often needed.<br>Surgical resection of CNS lesions may be beneficial. |
| ***Ancylostoma caninum*** | See EOSINOPHILIC COLITIS. | |
| ***Ancylostoma duodenale*** | See HOOKWORM. | |

## PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

| Disease/Organism | Treatment (evidence grade) | Comments |
|---|---|---|
| **ANGIOSTRONGYLIASIS**[11–14] | | |
| *Angiostrongylus cantonensis* | Supportive care | Most patients recover without antiparasitic therapy; treatment may provoke severe neurologic symptoms.<br>Corticosteroids, analgesics, and repeat lumbar puncture may be of benefit.<br>Prednisolone (60 mg daily for 2 wk) may shorten duration of headache and reduce need for repeat lumbar puncture.<br>Ocular disease may require surgery or laser treatment. |
| *Angiostrongylus costaricensis* (eosinophilic enterocolitis) | Supportive care | Surgery may be pursued to exclude another diagnosis such as appendicitis. |
| **ASCARIASIS** (*Ascaris lumbricoides*)[15] | First line: albendazole 400 mg PO once OR mebendazole 500 mg once; 100 mg tid for 3 days (no longer available in the US) (BII)<br>Pregnant women: pyrantel pamoate 11 mg/kg max 1 g once<br>Alternatives: ivermectin 150–200 µg/kg PO once (CII); nitazoxanide 7.5 mg/kg once | Follow-up stool ova and parasite examination after therapy not essential.<br>Take albendazole with food (bioavailability increases with food, especially fatty meals).<br>Albendazole has theoretical risk of causing seizures in patients coinfected with cysticercosis. |
| **BABESIOSIS** (*Babesia* spp)[16–18] | Clindamycin 30 mg/kg/day IV or PO div tid (max 600 mg per dose), PLUS quinine 25 mg/kg/day PO (max 650 mg/dose) div tid for 7–10 days (BII) (preferred for severe disease); OR atovaquone 40 mg/kg/day (max 750 mg/dose) div bid, PLUS azithromycin 12 mg/kg/day (max 500 mg/dose) for 7–10 days (CII) | Daily monitoring of hematocrit and percentage of parasitized red blood cells (until <5%) should be done.<br>Exchange blood transfusion may be of benefit for severe disease; *Babesia divergens.*<br>Higher doses of medications and prolonged therapy may be needed for asplenic or immunocompromised individuals.<br>Atovaquone and azithromycin preferred for mild disease due to more favorable adverse event profile. |

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| ***Balantidium coli***[19] | Tetracycline (patients >7 y) 40 mg/kg/day PO div qid for 10 days (max 2 g/day) (CII); OR metronidazole 35–50 mg/kg/day PO div tid for 5 days | Repeated stool examination may be needed for diagnosis; prompt stool examination may increase detection of rapidly degenerating trophozoites. Follow-up stool exam if symptoms continue.<br>Nitazoxanide may also be effective. |
| ***Baylisascaris procyonis*** (raccoon roundworm)[20,21] | For CNS infection: albendazole 50 mg/kg/day PO div q12h AND high-dose corticosteroid therapy (CIII) | Therapy generally unsuccessful to prevent fatal outcome or severe neurologic sequelae once CNS disease present.<br>Steroids may be of value in decreasing inflammation with therapy of CNS or ocular infection.<br>Retinal worms may be killed by direct photocoagulation.<br>Consider prophylactic albendazole (25–50 mg/kg PO daily for 20 days) for children who may have ingested soil contaminated with raccoon feces.<br>If albendazole not immediately available, ivermectin may be useful in the interim.<br>Albendazole bioavailability increased with food, especially fatty meals. |
| ***Blastocystis hominis***[22,23] | Metronidazole 30 mg/kg/day (max 750 mg per dose) PO div tid for 5–10 days (BII); OR tinidazole 50 mg/kg (max 2 g) once (age >3 years) (BII) | Pathogenesis debated. Asymptomatic individuals do not need treatment; diligent search for other pathogenic parasites recommended for symptomatic individuals with *B hominis*.<br>Paromomycin, nitazoxanide, and TMP/SMX also may be effective.<br>Metronidazole resistance may occur.<br>Take tinidazole with food; tablets may be crushed and mixed with flavored syrup. |
| **CHAGAS DISEASE** (*Trypanosoma cruzi*)[24–26] | See TRYPANOSOMIASIS. | |
| ***Clonorchis sinensis*** | See FLUKES. | |

## PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

| Disease/Organism | Treatment (evidence grade) | Comments |
|---|---|---|
| **CRYPTOSPORIDIOSIS** (*Cryptosporidium parvum*)[27–30] | Nitazoxanide, age 12–47 mo, 5 mL (100 mg) bid for 3 days; age 4–11 y, 10 mL (200 mg) bid for 3 days; age ≥12 y, 500 mg (tab or suspension) PO bid for 3 days (BII).<br>Paromomycin 30 mg/kg/day div bid–qid (CII); OR azithromycin 10 mg/kg/day for 5 days (CII); or paromomycin AND azithromycin given as combination therapy may yield initial response but may not result in sustained cure in immunocompromised individuals. | Recovery depends largely on the immune status of the host; treatment not required in all immunocompetent individuals.<br>Medical therapy may have limited efficacy in HIV-infected patients not receiving HAART. |
| **CUTANEOUS LARVA MIGRANS or CREEPING ERUPTION**[31,32] (dog and cat hookworm) (*Ancylostoma caninum, Ancylostoma braziliense, Uncinaria stenocephala*) | Albendazole 15 mg/kg/day (max 400 mg) PO qd for 3 days (CII); OR ivermectin 200 µg/kg PO for 1–2 days (CII) | Albendazole bioavailability increased with food, especially fatty meals |
| ***Cyclospora*** spp[33,34] (cyanobacterium-like agent) | TMP/SMX 10 mg TMP/kg/day (max 1 DS tablet) PO div bid for 7–10 days (BIII); OR nitazoxanide 500 mg bid | HIV-infected patients may require higher doses/longer therapy.<br>Ciprofloxacin 30 mg/kg/day div bid for 7 days is an alternative, although treatment failures have been reported. |
| **CYSTICERCOSIS**[35–37] (*Cysticercus cellulosae*) | Albendazole 15 mg/kg/day PO div bid (max 800 mg/day) for 15 days (CII); addition of dexamethasone (6 mg daily) for 10 days may reduce seizure risk; OR praziquantel 50 mg/kg/day PO div tid for 15 days (CII). | Management of seizures, edema, intracranial hypertension, or hydrocephalus, when present, is the focus of initial therapy.<br>Treatment regimens with antiparasitic therapy are evolving; involvement with specialist with experience treating this condition recommended.<br>Albendazole courses ranging from 7–30 days have been recommended depending on extent of disease. |

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| | | Treatment generally recommended for symptomatic patients with multiple live lesions; generally will not provide benefit when all lesions are calcified, although viable, live cysts may not be identified on MRI scans.<br>Intravesicular and intraocular cysts should be treated with surgical removal; antiparasitic therapy relatively contraindicated. |
| **DIENTAMEBIASIS**[38,39] (*Dientamoeba fragilis*) | Metronidazole 35–50 mg/kg/day PO div tid for 10 days (max 500–750 mg/dose); OR paromomycin 25–35 mg/kg/day PO div tid for 7 days; OR iodoquinol 30–40 mg/kg/day (max 650 mg/dose) PO div tid for 20 days (BII) | Treatment indicated when no other cause except *Dientamoeba* found for abdominal pain or diarrhea lasting more than a week.<br>Take paromomycin with meals and iodoquinol after meals.<br>Nitazoxanide may be effective.<br>Albendazole has no activity against *Dientamoeba.* |
| ***Diphyllobothrium latum*** | See TAPEWORMS. | |
| **ECHINOCOCCOSIS**[40,41] | | |
| *Echinococcus granulosus* | Albendazole 15 mg/kg/day PO div bid (max 800 mg/day) for 1–6 mo alone (CIII) or as adjunctive therapy with surgery or percutaneous treatment; initiate 4–30 days before and at least 1 mo after surgery. | Surgery is the treatment of choice for management of complicated cysts.<br>PAIR technique effective for appropriate cysts.<br>Praziquantel has protoscolicidal activity but clinical efficacy variable; may be used in combination therapy with albendazole |
| *Echinococcus multilocularis* | Surgical treatment generally the treatment of choice; postoperative albendazole (15 mg/kg/day PO div bid (max 800 mg/day) should be administered to reduce relapse; duration uncertain (at least 2 y with long monitoring for relapse).<br>Benefit of preoperative albendazole unknown. | |
| ***Entamoeba histolytica*** | See AMEBIASIS. | |

## PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

| Disease/Organism | Treatment (evidence grade) | Comments |
|---|---|---|
| ***Enterobius vermicularis*** | See PINWORMS. | |
| ***Fasciola hepatica*** | See FLUKES. | |
| **EOSINOPHILIC COLITIS**[42] (*Ancylostoma caninum, Angiostrongylus costaricensis*) | Albendazole 400 mg PO once (BIII) | Endoscopic removal may be considered if medical treatment not successful. |
| **EOSINOPHILIC MENINGITIS** | See ANGIOSTRONGYLIASIS. | |
| **FILARIASIS**[43,44] | | |
| – River blindness (*Onchocerca volvulus*) | Ivermectin 150 µg/kg PO once (AII); repeat q6–12mo until asymptomatic and no ongoing exposure; OR doxycycline 200 mg PO daily for 6 wk. | |
| – *Wuchereria bancrofti, Brugia malayi, Brugia timori, Mansonella streptocerca* | DEC (from CDC) 6 mg/kg/day div tid for 12 days OR 6 mg/kg/day PO as a single dose (AII).<br>Consider adding doxycycline 200 mg daily for 4–6 wk. | Avoid DEC with *Onchocerca* and *Loa loa* coinfection; albendazole may be used in these patients. |
| *Mansonella ozzardi* | Ivermectin 200 µg/kg PO once may be effective. | DEC not effective |
| *Mansonella perstans* | Albendazole 400 mg PO bid for 10 days | DEC and ivermectin not effective; doxycycline 200 mg daily for 6 wk beneficial for infection acquired in West Africa |
| *Loa loa* | When no evidence of microfilaremia: DEC (from CDC) 9 mg/kg/day PO div tid for 21 days<br>When microfilaremia present: day 1: 1 mg/kg (max 50 mg); day 2: 1 mg/kg (max 50 mg) div tid; day 3: 1–2 mg/kg (max 100 mg) div tid; days 4–21: 9 mg/kg/day PO div tid | Albendazole is an alternative agent. |
| Tropical pulmonary eosinophilia[45] | DEC (from CDC) 6 mg/kg/day PO div tid for 12–21 days; antihistamines/corticosteroids for allergic reactions (CII) | |

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| **FLUKES** | | |
| Chinese liver fluke[46] (*Clonorchis sinensis*) and others (*Fasciolopsis, Heterophyes, Metagonimus, Metorchis, Nanophyetus, Opisthorchis*) | Praziquantel 75 mg/kg PO div tid for 2 days (BII); OR albendazole 10 mg/kg/day PO for 7 days (CIII) | Take praziquantel with liquids and food. |
| Lung fluke[47,48] (*Paragonimus westermani* and other *Paragonimus* lung flukes) | Praziquantel 75 mg/kg PO div tid for 3 days (BII) | Triclabendazole (available from CDC) (10 mg/kg PO once or twice) may also be effective; triclabendazole should be taken with food to facilitate absorption. |
| Sheep liver fluke[49] (*Fasciola hepatica*) | Triclabendazole (from CDC) 10 mg/kg PO for 1–2 days (BII) OR nitazoxanide PO (take with food), age 12–47 mo, 100 mg/dose bid for 7 days; age 4–11 y, 200 mg/dose bid for 7 days; age ≥12 y, 1 tab (500 mg)/dose bid for 7 days (CII) | |
| **GIARDIASIS** (*Giardia intestinalis* [formerly *lamblia*])[50–52] | Metronidazole 15–30 mg/kg/day (max 250 mg/dose) PO div tid for 5–7 days (BII); OR nitazoxanide PO (take with food), age 1–3 y, 100 mg/dose bid for 3 days; age 4–11 y, 200 mg/dose bid for 3 days; age ≥12 y, 500 mg/dose bid for 3 days (BII); OR tinidazole 50 mg/kg/day (max 2 g) for 1 day (BII) | Alternatives: furazolidone 6 mg/kg/day in 4 doses for 7–10 days; OR paromomycin 30 mg/kg/day div tid for 5–10 days; OR albendazole 10–15 mg/kg/day (max 400 mg/dose) PO for 5 days (CII).<br>If therapy ineffective, may try a higher dose or longer course of the same agent, or an agent in a different class; combination therapy may be considered for refractory cases.<br>Prolonged courses may be needed for immunocompromised conditions (eg, hypogammaglobulinemia).<br>Treatment of asymptomatic carriers not usually recommended but may be requested by public health authorities. |

## PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

| Disease/Organism | Treatment (evidence grade) | Comments |
|---|---|---|
| **HOOKWORM**[53–55] | | |
| *Necator americanus, Ancylostoma duodenale* | Albendazole 400 mg once (repeat dose may be necessary) (BII); OR metronidazole 100 mg PO for 3 days; OR pyrantel pamoate 11 mg/kg (max 1 g/day) (BII) PO qd for 3 days | |
| *Ancylostoma caninum* | Albendazole 400 mg once | May be a cause of eosinophilic enteritis. |
| ***Hymenolepis nana*** | See TAPEWORMS. | |
| ***Cystoisospora belli*** (formerly *Isospora belli*)[19] | TMP/SMX 8–10 mg TMP/kg/day PO (or IV) div bid for 7–10 days (max 160 mg TMP/800 mg SMX twice daily); OR ciprofloxacin 500 mg PO div bid for 7 days | Infection often self-limited in immunocompetent hosts; consider treatment if symptoms do not resolve by 5–7 days or are severe.<br>Pyrimethamine plus leucovorin and nitazoxanide are alternatives.<br>Immunocompromised patients should be treated; longer courses or suppressive therapy may be needed for severely immunocompromised patients. |
| **LEISHMANIASIS,**[56–62] including kala-azar | | |
| *Leishmania* spp | Visceral: liposomal AmB 3 mg/kg/day on days 1–5, day 14, and day 21 (AI); OR sodium stibogluconate (from CDC) 20 mg/kg/day IM or IV for 28 days (or longer) (BIII); OR miltefosine 2.5 mg/kg/day PO (max 150 mg/day) for 28 days (BII); OR AmB 1 mg/kg/day IV daily for 15–20 days or qod for 4–8 wk (BIII).<br>Uncomplicated cutaneous: combination of debridement of eschars, cryotherapy, thermotherapy, intralesional pentavalent antimony, and topical paromomycin (not available in US). | Consultation with a specialist familiar with management of leishmaniasis is advised, especially when treating patients with HIV coinfection.<br>Region where infection acquired and species of *Leishmania* affect therapeutic options.<br>Combination therapies may provide additional therapeutic options.<br>For immunocompromised patients, FDA-approved dosing of liposomal amphotericin is 4 mg/kg on days 1–5, 10, 17, 24, 31, and 38, with further therapy on an individual basis. |

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| | Complicated cutaneous: parenteral or oral systemic therapy with sodium stibogluconate 20 mg/kg/day IM or IV for 10–20 days (BIII); OR miltefosine (as above) (BII); OR pentamidine isethionate 2–4 mg/kg/day IV or IM daily or qod for 4–7 doses or until healed (BII); OR amphotericin 0.5–1 mg/kg IV qod for 20–30 days; OR azoles (efficacy is limited and treatment failure common).<br>Mucosal: sodium stibogluconate 20 mg/kg/day IM or IV for 28 days; OR AmB 0.5–1 mg/kg/day IV daily for 15–20 days or qod for 4–8 wk; OR miltefosine 2.5 mg/kg/day PO (max 150 mg/day) for 28 days. | |
| **LICE** | | |
| *Pediculus capitis* or *humanus, Phthirus pubis*[63] | Follow manufacturer's instructions for topical use: permethrin 1% OR pyrethrin (both preferred with piperonyl butoxide for children aged ≥2 y) (BII); OR 0.5% ivermectin lotion (BII); OR spinosad 0.9% topical suspension (BII); OR benzyl alcohol lotion 5% (BIII); OR malathion 0.5% (BIII); OR for topical therapies repeat in 1 wk; OR ivermectin 200 µg/kg PO once (400 µg/kg for ≥15 kg) | Launder bedding and clothing; for eyelash infestation, use petrolatum; for head lice, remove nits with comb designed for that purpose.<br>Use benzyl alcohol lotion and ivermectin lotion for children aged ≥6 mo, spinosad for aged ≥4 y, and malathion for aged ≥6 y.<br>Benzyl alcohol can be irritating to skin; parasite resistance unlikely to develop.<br>Consult health care professional before re-treatment with ivermectin lotion; re-treatment with spinosad topical suspension usually not needed unless live lice seen 1 wk after treatment.<br>Administration of 3 doses of ivermectin (1 dose/wk separately by weekly intervals) may be needed to eradicate heavy infection. |

## PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

| Disease/Organism | Treatment (evidence grade) | Comments |
|---|---|---|
| **MALARIA**[64–68] | | |
| *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae* | CDC Malaria Hotline 770/488-7788 or 855/856-4713 toll-free (Monday–Friday, 9:00 am–5:00 pm ET) or emergency consultation after hours 770/488-7100; online information at www.cdc.gov/malaria (accessed September 1, 2015). Consult tropical medicine specialist if unfamiliar with malaria. | No antimalarial drug provides absolute protection against malaria; fever after return from an endemic area should prompt an immediate evaluation.<br>Emphasize personal protective measures (insecticides, bed nets, clothing, and avoidance of dusk–dawn mosquito exposures). |
| **Prophylaxis** | | |
| For areas with chloroquine-resistant *P falciparum* or *P vivax* | A-P: 5–8 kg, ½ pediatric tab/day; ≥9–10 kg, ¾ pediatric tab/day; ≥11–20 kg, 1 pediatric tab (62.5 mg atovaquone/25 mg proguanil); ≥21–30 kg, 2 pediatric tabs; ≥31–40 kg, 3 pediatric tabs; ≥40 kg, 1 adult tab (250 mg atovaquone/100 mg proguanil) PO daily starting 1–2 days before travel and continuing 7 days after last exposure; for children <5 kg, data on A-P limited (BII); OR mefloquine: for children <5 kg, 5 mg/kg; ≥5–9 kg, 1/8 tab; ≥10–19 kg, ¼ tab; 20–30 kg, ½ tab; ≥31–45 kg, ¾ tab; ≥45 kg (adult dose), 1 tab PO once weekly starting the wk before arrival in area and continuing for 4 wk after leaving area (BII); OR doxycycline (patients >7 y): 2 mg/kg (max 100 mg) PO daily starting 1–2 days before arrival in area and continuing for 4 wk after leaving area (BIII); OR primaquine (check for G6PD deficiency before administering): 0.5 mg/kg base daily starting 1 day before travel and continuing for 5 days after last exposure (BII) | Avoid mefloquine for persons with a history of seizures or psychosis, active depression, or cardiac conduction abnormalities; see black box warning.<br>Avoid A-P in severe renal impairment (CrCl <30).<br>*P falciparum* resistance to mefloquine exists along the borders between Thailand and Myanmar and Thailand and Cambodia, Myanmar and China, and Myanmar and Laos; isolated resistance has been reported in southern Vietnam.<br>Take doxycycline with adequate fluids to avoid esophageal irritation and food to avoid GI side effects; use sunscreen and avoid excessive sun exposure. |

| | | |
|---|---|---|
| For areas without chloroquine-resistant *P falciparum* or *P vivax* | Chloroquine phosphate 5 mg base/kg (max 300 mg base) PO once weekly, beginning the wk before arrival in area and continuing for 4 wk after leaving area (available in suspension outside the US and Canada) (All).<br>For heavy or prolonged (months) exposure to mosquitoes: consider treating with primaquine (check for G6PD deficiency before administering) 0.5 mg base/kg PO qd with final 2 wk of chloroquine for prevention of relapse with *P ovale* or *P vivax*. | |
| **Treatment of disease** | | Consider exchange blood transfusion for >10% parasitemia, altered mental status, pulmonary edema, or renal failure. |

## PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

| Disease/Organism | Treatment (evidence grade) | Comments |
|---|---|---|
| – Chloroquine-resistant *P falciparum* or *P vivax* | Oral therapy: artemether/lumefantrine 6 doses over 3 days at 0, 8, 24, 36, 48, and 60 h; <15 kg, 1 tab/dose; ≥15–25 kg, 2 tabs/dose; ≥25–35 kg, 3 tabs/dose; ≥35 kg, 4 tabs/dose (BII); A-P: for children <5 kg, data limited; ≥5–8 kg, 2 pediatric tabs (62.5 mg atovaquone/25 mg proguanil) PO qd for 3 days; ≥9–10 kg, 3 pediatric tabs qd for 3 days; ≥11–20 kg, 1 adult tab (250 mg atovaquone/100 mg proguanil) qd for 3 days; ≥21–30 kg, 2 adult tabs qd for 3 days; 31–40 kg, 3 adult tabs qd for 3 days; ≥40 kg, 4 adult tabs qd for 3 days (BII); OR quinine 30 mg/kg/day (max 2 g/day) PO div tid for 3–7 days AND doxycycline (age >7 y) 4 mg/kg/day div bid for 7 days OR clindamycin 30 mg/kg/day div tid (max 900 mg tid) for 7 days.<br>Parenteral therapy (check with CDC): quinidine 10 mg/kg (max 600 mg) IV (1 h infusion in normal saline) followed by continuous infusion of 0.02 mg/kg/min until oral therapy can be given (after 48-h therapy, decrease dose by 1/3 to ½) (BII); alternative: artesunate 2.4 mg/kg/dose IV for 3 days at 0, 12, 24, 48, and 72 h (from CDC) (BI) AND a second oral agent (A-P, clindamycin, or doxycycline for aged ≥7 y).<br>For prevention of relapse with *P vivax, P ovale:* primaquine (check for G6PD deficiency before administering) 0.5 mg base/kg/day PO for 14 days. | Mild disease may be treated with oral antimalarial drugs; severe disease (impaired level of consciousness, convulsion, hypotension, or parasitemia >5%) should be treated parenterally.<br>Avoid mefloquine for treatment of malaria if possible given higher dose and increased incidence of adverse events.<br>Take clindamycin and doxycycline with plenty of liquids.<br>Do not use primaquine during pregnancy.<br>For relapses of primaquine-resistant *P vivax* or *P ovale,* consider retreating with primaquine 30 mg (base) for 28 days.<br>Continuously monitor ECG, BP, and glucose in patients receiving quinidine.<br>Avoid artemether/lumefantrine and mefloquine in patients with cardiac arrhythmias, and avoid concomitant use of drugs that prolong QT interval.<br>Take A-P and artemether/lumefantrine with food or milk.<br>Use artesunate for quinidine intolerance, lack of quinidine availability, or treatment failure; www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf (accessed September 1, 2015); artemisinin should be used in combination with other drugs to avoid resistance. |
| – Chloroquine-susceptible *P falciparum,* chloroquine-susceptible *P vivax, P ovale, P malariae* | Oral therapy: chloroquine 10 mg/kg base (max 600 mg base) PO then 5 mg/kg 6, 24, and 48 h after initial dose.<br>Parenteral therapy: quinidine, as above. | |

| | | |
|---|---|---|
| | See above for prevention of relapse due to *P vivax* and *P ovale.* | |
| ***Paragonimus westermani*** | See FLUKES. | |
| **PINWORMS** (*Enterobius vermicularis*) | Albendazole: <20 kg, 200 mg PO once; ≥20 kg, 400 mg PO once; repeat in 2 wk (BII); OR pyrantel pamoate 11 mg/kg (max 1 g) PO once (BII); repeat in 2 wk. | Treatment of entire household (and if this fails, consider close child care/school contacts) often recommended; re-treatment of contacts after 2 wk may be needed to prevent reinfection. |
| ***PNEUMOCYSTIS*** | See Chapter 8, Table 8B, *Pneumocystis jiroveci* (*carinii*) pneumonia. | |
| **SCABIES** (*Sarcoptes scabiei*)[69] | Permethrin 5% cream applied to entire body (including scalp in infants), left on for 8–14 h then bathe, repeat in 1 wk (BII); OR ivermectin 200 µg/kg PO once weekly for 2 doses (BII); OR crotamiton 10% applied topically overnight on days 1, 2, 3, and 8, bathe in am (BII). | Launder bedding and clothing.<br>Reserve lindane for patients who do not respond to other therapy.<br>Crotamiton treatment failure has been observed.<br>Ivermectin safety not well established in children <15 kg and pregnant women. |
| **SCHISTOSOMIASIS** (*Schistosoma haematobium, Schistosoma japonicum, Schistosoma mansoni, Schistosoma mekongi, Schistosoma intercalatum*)[70–72] | Praziquantel 40 (for *S haematobium, S mansoni,* and *S intercalatum*) or 60 (for *S japonicum* and *S mekongi*) mg/kg/d PO div bid (if 40 mg/day) or tid (if 60 mg/day) for 1 day (AI) | Take praziquantel with food and liquids.<br>Oxamniquine (not available in the US) 20 mg/kg PO div bid for 1 day (Brazil) or 40–60 mg/kg/day for 2–3 days (most of Africa) (BII). |
| **STRONGYLOIDIASIS** (*Strongyloides stercoralis*)[73,74] | Ivermectin 200 µg/kg PO qd for 1–2 days (BI); OR albendazole 400 mg PO bid for 7 days (or longer for disseminated disease) (BII) | Albendazole is less effective but may be adequate if longer courses used.<br>For immunocompromised patients (especially with hyperinfection syndrome), parenteral veterinary formulations may be lifesaving.<br>Safety of ivermectin in children <15 kg and pregnant women yet to be well established. |

## PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

| Disease/Organism | Treatment (evidence grade) | Comments |
|---|---|---|
| **TAPEWORMS** | | |
| – *Cysticercus cellulosae* | See CYSTICERCOSIS. | |
| – *Echinococcus granulosus* | See ECHINOCOCCOSIS. | |
| – *Taenia saginata, Taenia solium, Hymenolepis nana, Diphyllobothrium latum, Dipylidium caninum* | Praziquantel 5–10 mg/kg PO once (25 mg/kg once for *H nana*) (BII); OR niclosamide 50 mg/kg (max 2 g) PO once, chewed thoroughly (all but *H nana*) | Limited availability of niclosamide in US; may be available in compounding pharmacies.<br>Nitazoxanide may be effective (published clinical data limited). |
| **TOXOCARIASIS**[75] (*Toxocara canis* [dog roundworm] and *Toxocara cati* [cat roundworm]) | Visceral larval migrans: Albendazole 400 mg PO bid for 5 days (BII)<br>Ocular larva migrants: Albendazole 400 mg PO daily (800 mg daily for adults) for 2–4 wk with prednisone (0.5–1 mg/kg/day with slow taper) | Corticosteroids may be used for severe symptoms in visceral larval migrans.<br>Mebendazole (not available in the US) and DEC (available only from CDC) are alternatives. |
| **TOXOPLASMOSIS** (*Toxoplasma gondii*)[76–78] | Pyrimethamine 2 mg/kg/day PO div bid for 2 days (max 100 mg) then 1 mg/kg/day (max 25 mg/day) PO daily AND sulfadiazine 120 mg/kg/day PO div qid (max 6 g/day); with supplemental folinic acid and leucovorin 10–25 mg with each dose of pyrimethamine (AI) for 3–6 wk.<br>See Chapter 5 for congenital infection.<br>For treatment in pregnancy, spiramycin 50–100 mg/kg/day PO div qid (available as investigational therapy through the FDA at 301/796-0563) (CII). | Treatment continued for 2 wk after resolution of illness (approximately 3–6 wk); concurrent corticosteroids given for ocular or CNS infection. Prolonged therapy if HIV positive.<br>Take pyrimethamine with food to decrease GI adverse effects; sulfadiazine should be taken on an empty stomach with water.<br>Atovaquone or clindamycin plus pyrimethamine may be effective for patients intolerant of sulfa-containing drugs.<br>Consult expert advice for treatment during pregnancy and management of congenital infection. |
| **TRAVELER'S DIARRHEA**[79–81] | Azithromycin 10 mg/kg qd for 3–5 days (BII); OR rifaximin 200 mg PO tid for 3 days (ages ≥12 y) (BIII); OR ciprofloxacin (BII); OR cefixime (CII) | Azithromycin preferable to ciprofloxacin for travelers to Southeast Asia given high prevalence of quinolone-resistant *Campylobacter.* |

| | | |
|---|---|---|
| | | Rifaximin may not be as efficacious for *Shigella* and other enterics in patients with bloody diarrhea and invasive infection. |
| **TRICHINELLOSIS** (*Trichinella spiralis*)[82] | Albendazole 20 mg/kg/day (max 400 mg/dose) PO div bid for 8–14 days (BII) | Therapy ineffective for larvae already in muscles.<br>Anti-inflammatory drugs, steroids for CNS or cardiac involvement or severe symptoms. |
| **TRICHOMONIASIS** (*Trichomonas vaginalis*) | Tinidazole 50 mg/kg (max 2 g) PO for 1 dose (BII) OR metronidazole 500 mg PO tid for 7 days (BII) | Treat sex partners simultaneously.<br>Metronidazole resistance occurs and may be treated with higher-dose metronidazole or tinidazole. |
| ***Trichuris trichiura*** | See WHIPWORM (TRICHURIASIS). | |
| **TRYPANOSOMIASIS** | | |
| – Chagas disease[24] (*Trypanosoma cruzi*) | Benznidazole PO (from CDC): age <12 y, 5–7.5 mg/kg/day div bid for 60 days; ≥12 y, 5–7 mg/kg/day div bid for 60 days (BIII); OR nifurtimox PO (from CDC): age 1–10 y, 15–20 mg/kg/day div tid or qid for 90 days; 11–16 y, 12.5–15 mg/kg/day div tid or qid for 90 days; ≥17 y, 8–10 mg/kg/day div tid–qid for 90–120 days (BIII) | Therapy recommended for acute and congenital infection, reactivated infection, and chronic infection in children aged <18 y; consider in those up to age 50 with chronic infection without advanced cardiomyopathy.<br>Side effects fairly common.<br>Both drugs contraindicated in pregnancy. |
| – Sleeping sickness[83–86] (*Trypanosoma brucei gambiense* [West African]; *T brucei rhodesiense* [East African]; acute [hemolymphatic] stage) | *Tb gambiense:* pentamidine isethionate 4 mg/kg/day (max 300 mg) IM or IV for 7–10 days (BII)<br>*Tb rhodesiense:* suramin (from CDC) 100–200 mg test dose IV, then 20 mg/kg (max 1 g) IV on days 1, 3, 5, 14, and 21 (BII) | Consult with tropical medicine specialist if unfamiliar with trypanosomiasis.<br>Examination of the buffy coat of peripheral blood may be helpful.<br>*Tb gambiense* may be found in lymph node aspirates. |

## PREFERRED THERAPY FOR SPECIFIC PARASITIC PATHOGENS (continued)

| Disease/Organism | Treatment (evidence grade) | Comments |
|---|---|---|
| Late (CNS) stage | *Tb gambiense:* eflornithine (from CDC) 400 mg/kg/day IV div bid for 7 days PLUS nifurtimox 5 mg/kg PO tid for 10 days (BIII); OR eflornithine 400 mg/kg/day IV div qid for 14 days; OR melarsoprol (from CDC) 2.2 mg/day (max 180 mg) IV for 10 days (BIII).<br>*Tb rhodesiense:* melarsoprol, 2–3.6 mg/kg/day IV for 3 days; after 7 days, 3.6 mg/kg/day for 3 days; after 7 days, 3.6 mg/kg/day for 3 days; corticosteroids often given with melarsoprol to decrease risk of CNS toxicity. | CSF examination needed for management (double-centrifuge technique recommended); perform repeat CSF examinations every 6 mo for 2 y to detect relapse. |
| **VISCERAL LARVA MIGRANS (TOXOCARIASIS)** | | |
| *Toxocara canis; Toxocara cati* | Visceral larval migrans: albendazole 400 mg PO bid for 5 days (BII)<br>Ocular larva migrants: albendazole 400 mg PO daily (800 mg daily for adults) for 2–4 wk with prednisone (0.5–1 mg/kg/day with slow taper) | Corticosteroids may be used for severe symptoms in visceral larva migrans.<br>Mebendazole (not available in the US) and DEC (available only from CDC) are alternatives. |
| **WHIPWORM (TRICHURIASIS)** | | |
| *Trichuris trichiura* | Albendazole 400 mg PO for 3 days; OR ivermectin 200 µg/kg/day PO daily for 3 days (BII); OR mebendazole 100 mg PO bid for 3 days | Mebendazole is not available in the US.<br>Treatment can be given for 5–7 days for heavy infestation. |
| ***Wuchereria bancrofti*** | See FILARIASIS. | |
| **Yaws** | Azithromycin 30 mg/kg maximum 2 g once (also treats bejel and pinta) | Alternative regimens include IM benzathine benzylpenicillin and the second line agents doxycycline, tetracycline, and erythromycin. |

## 11. Alphabetic Listing of Antimicrobials

### NOTES

- Higher dosages in a dose range are generally indicated for more serious infections. For pathogens with higher minimal inhibitory concentrations against beta-lactam antibiotics, a more prolonged infusion of the antibiotic will allow increased antibacterial effect (see Chapter 3).
- Maximum dosages for adult-sized children (eg, >40 kg) are based on US Food and Drug Administration (FDA)-approved product labeling or post-marketing data.
- For information on dosing in children who are obese, see Chapter 12.
- Antiretroviral medications are not included. See Chapter 9.
- Drugs with FDA-approved dosage, or dosages based on randomized clinical trials, are given a Level of Evidence I. Dosages for which data are collected, from non-comparative trials, or from small comparative trials, are given a Level of Evidence II. Dosages based on expert or consensus opinion or case reports are given a Level of Evidence III.
- If no oral liquid form is available, round the child's dose to a combination of available solid dosage forms. Consult a pediatric pharmacist for recommendations on mixing with food (crushing tablets, emptying capsule contents) and the availability of extemporaneously compounded liquid formulations.
- Cost estimates in US dollars per course, or per month for continual regimens, are provided. Estimates are based on prices at the editor's institution. These may differ from that of the reader due to contractual differences, regional market forces, and supply fluctuations. Legend: $ = <$100, $$ = $100–$400, $$$ = $401–$1,000, $$$$ = >$1,000, $$$$$ = >$10,000.
- There are some agents that we do not recommend even though they may be available. We believe they are significantly inferior to those we do recommend (see Chapters 5–10) and could possibly lead to poor outcomes if used. Such agents are not listed.
- **Abbreviations:** AOM, acute otitis media; bid, twice daily; BSA, body surface area; CABP, community-acquired bacterial pneumonia; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus;* cap, capsule or caplet; CDC, Centers for Disease Control and Prevention; CF, cystic fibrosis; CMV, cytomegalovirus; CNS, central nervous system; CrCl, creatinine clearance; div, divided; DR, delayed release; EC, enteric coated; ER, extended release; FDA, US Food and Drug Administration; hs, bedtime; HSV, herpes simplex virus; IBW, ideal body weight; IM, intramuscular; IV, intravenous; IVPB, IV piggyback (premixed bag); LD, loading dose; MAC, *Mycobacterium avium* complex; MRSA, methicillin-resistant *S aureus;* NS, normal saline; oint, ointment; ophth, ophthalmic; PCP, *Pneumocystis* pneumonia; PIP, piperacillin; PMA, post-menstrual age; PO, oral; pwd, powder; qd, once daily; qhs, every bedtime;

qid, 4 times daily; RSV, respiratory syncytial virus; SIADH, syndrome of inappropriate antidiuretic hormone; SMX, sulfamethoxazole; soln, solution; SPAG-2, small particle aerosol generator model-2; SQ, subcutaneous; supp, suppository; susp, suspension; tab, tablet; TB, tuberculosis; TBW, total body weight; tid, 3 times daily; TMP, trimethoprim; top, topical; UTI, urinary tract infection; vag, vaginal; VZV, varicella-zoster virus.

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Acyclovir,[a] Zovirax | 500-, 1,000-mg vial ($) | IV | 15–45 mg/kg/day (I) (See Chapter 9.)<br>Max 1,500 mg/m$^2$/day (II) (See Chapter 12.) | q8h |
| | 200-mg/5-mL susp ($$)<br>200-mg cap ($)<br>400-, 800-mg tab ($) | PO | 900 mg/m$^2$/day (I)<br>60–80 mg/kg/day, max 4 g/day (I)<br>(See Chapters 5 and 9.) | q8h<br>q6–8h |
| Sitavig | 50-mg tab ($$) | Buccal | Adults 50 mg, for herpes labialis | One time |
| Albendazole, Albenza | 200-mg tab ($$$$) | PO | 15 mg/kg/day, max 800 mg/day (I) | q12h |
| Amikacin,[a] Amikin | 250 mg/mL in 2 or 4 mL vials ($$) | IV, IM | 15–22.5 mg/kg/day[c] (I) (See Chapter 1.)<br>30–35 mg/kg/day[c] for CF (II) | q8–24h<br>q24h |
| | | Intravesical | 50–100 mL of 0.5 mg/mL in NS (III) | q12h |
| Amoxicillin,[a] Amoxil | 125-, 200-, 250-, 400-mg/5-mL susp ($)<br>125-, 250-mg chew tab ($)<br>250-, 500-mg cap ($)<br>500-, 875-mg tab ($) | PO | Standard dose: 40–45 mg/kg/day (I)<br>High dose: 80–90 mg/kg/day (I)<br>150 mg/kg/day for penicillin-resistant *S pneumoniae* otitis media (III)<br>Max 4 g/day (III) | q8–12h<br>q12h<br>q8h |
| Amoxicillin extended release,[a] Moxatag | 775-mg tab ($$) | PO | ≥12 y and adults 775 mg/day | q24h |

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Amoxicillin/clavulanate,[a] Augmentin | 16:1 (Augmentin XR): 1,000/62.5-mg tab ($$) | PO | 16:1 formulation: ≥40 kg and adults 4,000 mg amoxicillin component/day (I) | q12h |
| | 14:1 (Augmentin ES): 600/42.9-mg/5-mL susp ($) | PO | 14:1 formulation: 90-mg amoxicillin component/kg/day (I), max 4 g/day (III) | q12h |
| | 7:1 (Augmentin): 875/125-mg tab; 200/28.5-, 400/57-mg chew tab; 200/28.5-, 400/57-mg/5-mL susp ($) | PO | 7:1 formulation: 25- to 45-mg amoxicillin component/kg/day, max 1,750 mg/day (I) | q12h |
| | 4:1 formulation: 500/125-mg tab; 125/31.25-, 250/62.5-mg chew tab; 125/31.25-, 250/62.5-mg/5-mL susp ($) | PO | 20- to 40-mg amoxicillin component/kg/day (max 1,500 mg/day) (I) | q8h |
| Amphotericin B deoxycholate,[a] Fungizone | 50-mg vial ($) | IV | 1–1.5 mg/kg pediatric and adults (I), no max<br>0.5 mg/kg for *Candida* esophagitis or cystitis (II) | q24h |
| | | Intravesical | 50–100 µg/mL in sterile water x 50–100 mL (III) | q8h |
| Amphotericin B, lipid complex, Abelcet | 100-mg/20-mL vial ($$$$) | IV | 5 mg/kg pediatric and adult dose (I)<br>No max | q24h |
| Amphotericin B, liposomal, AmBisome | 50-mg vial ($$$$) | IV | 5 mg/kg pediatric and adult dose (I)<br>No max | q24h |
| Ampicillin/ampicillin trihydrate[a] | 250-, 500-mg cap ($)<br>125-, 250-mg/5-mL susp ($) | PO | 50–100 mg/kg/day if <20 kg (I)<br>≥20 kg and adults 1–2 g/day (I) | q6h |
| Ampicillin sodium[a] | 125-, 250-, 500-mg vial ($)<br>1-, 2-, 10-g vial ($$) | IV, IM | 50–200 mg/kg/day, max 8 g/day (I) | q6h |
| | | | 300–400 mg/kg/day, max 12 g/day endocarditis/meningitis (III) | q4–6h |

| | | | | |
|---|---|---|---|---|
| Ampicillin/sulbactam,[a] Unasyn | 1/0.5-, 2/1-, 10/5-g vial ($) | IV, IM | 200-mg ampicillin component/kg/day (I)<br>≥40 kg and adults 4–max 8 g/day (I) | q6h |
| Anidulafungin, Eraxis | 50-, 100-mg vial ($$) | IV | 1.5–3 mg/kg LD, then 0.75–1.5 mg/kg (II)<br>Max 200-mg LD, then 100 mg (I) | q24h |
| Atovaquone,[a] Mepron | 750-mg/5-mL susp ($$$) | PO | 30 mg/kg/day if 1–3 mo or >24 mo (I)<br>45 mg/kg/day if 4–24 mo (I)<br>Max 1,500 mg/day (I) | q12h<br>q24h for prophylaxis |
| Atovaquone and proguanil,[a] Malarone | 62.5/25-mg pediatric tab ($$)<br>250/100-mg adult tab ($$$) | PO | Prophylaxis for malaria: 11–20 kg: 1 pediatric tab, 21–30 kg: 2 pediatric tabs, 31–40 kg: 3 pediatric tabs, >40 kg: 1 adult tab (I)<br>Treatment: 5–8 kg: 2 pediatric tabs, 9–10 kg: 3 pediatric tabs, 11–20 kg: 1 adult tab, 21–30 kg: 2 adult tabs, 31–40 kg: 3 adult tabs, >40 kg: 4 adult tabs (I) | q24h |
| Azithromycin,[a] Zithromax | 250-, 500-, 600-mg tab ($)<br>100-, 200-mg/5-mL susp ($) | PO | Otitis: 10 mg/kg/day for 1 day, then 5 mg/kg for 4 days; or 10 mg/kg/day for 3 days; or 30 mg/kg once (I).<br>Pharyngitis: 12 mg/kg/day for 5 days (I).<br>Sinusitis: 10 mg/kg/day for 3 days (I).<br>CABP: 10 mg/kg for 1 day, then 5 mg/kg/day for 4 days or 60 mg/kg once of ER (Zmax) susp, max 2 g (I).<br>Total cumulative dose max 2.5 g (I).<br>MAC prophylaxis: 5 mg/kg/day, max 250 mg (I), or 20 mg/kg, max 1.2 g qwk.<br>See Chapter 6 for other specific disease dosing recommendations. | q24h |
| Azithromycin, Zmax | 2-g/60-mL ER susp (Zmax) ($$) | | | |
| | 500-mg vial[a] ($) | IV | 10 mg/kg, max 500 mg (II) | q24h |
| Aztreonam,[a] Azactam | 1-, 2-g vial ($$) | IV, IM | 90–120 mg/kg/day, max 8 g/day (I) | q6–8h |
| Capreomycin, Capastat | 1-g vial ($$$$) | IV, IM | 15–30 mg/kg (III), max 1 g (I) | q24h |

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Caspofungin, Cancidas | 50-, 70-mg vial ($$$$) | IV | Load with 70 mg/m$^2$ once, then 50 mg/m$^2$, max 70 mg (I) | q24h |
| Cefaclor,[a] Ceclor | 125-, 250-, 375-mg/5-mL susp ($$)<br>250-, 500-mg cap ($)<br>500-mg ER tab ($$) | PO | 20–40 mg/kg/day, max 1 g/day (I) | q12h |
| Cefadroxil,[a] Duricef | 250-, 500-mg/5-mL susp ($)<br>500-mg cap ($)<br>1-g tab ($) | PO | 30 mg/kg/day, max 2 g/day (I) | q12–24h |
| Cefazolin,[a] Ancef | 0.5-, 1-, 10-, 20-g vial ($) | IV, IM | 25–100 mg/kg/day (I) | q8h |
| | | | 100–150 mg/kg/day for serious infections (III), max 12 g/day | q6h |
| Cefdinir,[a] Omnicef | 125-, 250-mg/5-mL susp ($)<br>300-mg cap ($) | PO | 14 mg/kg/day, max 600 mg/day (I) | q24h |
| Cefditoren, Spectracef | 200-, 400-mg tab ($$) | PO | ≥12 y and adults 400–800 mg/day (I) | q12h |
| Cefepime,[a] Maxipime | 1-, 2-g vial ($$) | IV, IM | 100 mg/kg/day, max 4 g/day (I) | q12h |
| | | | 150 mg/kg/day empiric therapy of fever with neutropenia, max 6 g/day (I) | q8h |
| Cefixime, Suprax | 100-, 200-mg/5-mL susp[a] ($$)<br>100-, 200-mg chew tab ($$)<br>400-mg cap ($$) | PO | 8 mg/kg/day, max 400 mg/day (I) | q24h |
| | | | For convalescent oral therapy of serious infections, up to 20 mg/kg/day (III) | q12h |
| Cefotaxime,[a] Claforan | 0.5-, 1-, 2-, 10-g vial ($) | IV, IM | 150–180 mg/kg/day, max 8 g/day (I) | q8h |
| | | | 200–225 mg/kg/day for meningitis, max 12 g/day (I) | q6h |

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|---|---|---|---|---|
| Cefotetan,[a] Cefotan | 1-, 2-, 10-g vial ($$)<br>1-, 2-g IVPB ($$) | IV, IM | 60–100 mg/kg/day (II), max 6 g/day (I) | q12h |
| Cefoxitin,[a] Mefoxin | 1-, 2-, 10-g vial ($)<br>1-, 2-g IVPB ($) | IV, IM | 80–160 mg/kg/day, max 12 g/day (I) | q6–8h |
| Cefpodoxime,[a] Vantin | 50-, 100-mg/5-mL susp ($)<br>100-, 200-mg tab ($) | PO | 10 mg/kg/day, max 400 mg/day (I) | q12h |
| Cefprozil,[a] Cefzil | 125-, 250-mg/5-mL susp ($)<br>250-, 500-mg tab ($) | PO | 15–30 mg/kg/day, max 1 g/d (I) | q12h |
| Ceftaroline, Teflaro (Doses are investigational in children.) | 400-, 600-mg vial ($$$$) | IV | <6 mo (II):<br>24 mg/kg/day for skin or CABP<br>30 mg/kg/day for complicated CABP<br>≥6 mo (II):<br>36 mg/kg/day for skin or CABP, max 1.2 g/day<br>45 mg/kg/day for complicated CABP, max 1.8 g/day | q8h |
| Ceftazidime,[a] Ceptaz, Fortaz | 0.5-, 1-, 2-, 6-g vial ($)<br>1-, 2-g IVPB ($) | IV, IM | 90–150 mg/kg/day, max 6 g/day (I) | q8h |
| | | IV | 200–300 mg/kg/day for serious *Pseudomonas* infection, max 12 g/day (II) | q8h |
| Ceftazidime/avibactam, Avycaz | 2 g/0.5 g vial ($$$$) | IV | Adults 7.5 g (6 g/1.5 g)/day (I)<br>NOTE: Pediatric dosing currently being used for phase 3 clinical trials: https://clinicaltrials.gov/ct2/show/NCT02497781?term=ceftazidime+avibactam&rank=11 | q8h |
| Ceftibuten,[a] Cedax | 180-mg/5-mL susp ($$$)<br>400-mg cap ($$$) | PO | 9 mg/kg/day, max 400 mg/day (I) | q24h |
| Ceftolozane/tazobactam, Zerbaxa | 1.5-g (1-g/0.5-g) vial ($$$$) | IV | Adults 4.5 g (3 g/1.5 g)/day (I) | q8h |

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Ceftriaxone,[a] Rocephin | 0.25-, 0.5-, 1-, 2-, 10-g vial ($) | IV, IM | 50 mg/kg, max 1 g, 1–3 doses IM for AOM (II)<br>50–75 mg/kg/day, max 2 g/day (I)<br>100 mg/kg/day for meningitis, max 4 g/day (I) | q24h<br>q24h<br>q12h |
| Cefuroxime axetil, Ceftin | 125-, 250-mg/5-mL susp ($$)<br>250-, 500-mg tab[a] ($) | PO | 20–30 mg/kg/day, max 1 g/day (I)<br>For bone and joint infections, up to 100 mg/kg/day, max 3 g/day (III) | q12h<br>q8h |
| Cefuroxime sodium,[a] Zinacef | 0.75-, 1.5-, 7.5-g vial ($) | IV, IM | 100–150 mg/kg/day, max 6 g/day (I) | q8h |
| Cephalexin,[a] Keflex | 125-, 250-mg/5-mL susp ($)<br>250-, 500-mg cap ($)<br>250-, 500-mg tab ($) | PO | 25–50 mg/kg/day (I) | q12h |
| | | | 75–100 mg/kg/day for bone and joint, or severe infections (II), max 4 g/day (I) | q6–8h |
| Chloroquine phosphate,[a] Aralen | 250-, 500-mg (150-, 300-mg base) tabs ($$) | PO | See Chapter 10. | |
| Cidofovir,[a] Vistide | 375-mg/5-mL vial ($$$) | IV | 5 mg/kg (III); see also Chapter 9. | Weekly |
| Ciprofloxacin,[a] Cipro | 250-, 500-mg/5-mL susp ($)<br>100-, 250-, 500-, 750-mg tab ($) | PO | 20–40 mg/kg/day, max 1.5 g/day (I) | q12h |
| | 200-, 400-mg vial ($)<br>200-, 400-mg IVPB ($) | IV | 20–30 mg/kg/day, max 1.2 g/day (I) | q12h |
| Ciprofloxacin extended release,[a] Cipro XR | 500-, 1,000-mg ER tab ($) | PO | Adults 500–1,000 mg (I) | q24h |
| Clarithromycin,[a] Biaxin | 125-, 250-mg/5-mL susp ($)<br>250-, 500-mg tab ($) | PO | 15 mg/kg/day, max 1 g/day (I) | q12h |

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|---|---|---|---|---|
| Clarithromycin extended release,[a] Biaxin XL[a] | 500-, 1,000-mg ER tab ($) | PO | Adults 1,000 mg (I) | q24h |
| Clindamycin,[a] Cleocin | 75 mg/5-mL soln ($$)<br>75-, 150-, 300-mg cap ($) | PO | 10–25 mg/kg/day, max 1.8 g/day (I)<br>30–40 mg/kg/day for CA-MRSA, intra-abdominal infection, or AOM (III) | q8h |
| | 0.3-, 0.6-, 0.9-g vial ($$)<br>0.3-, 0.6-, 0.9-g IVPB ($$) | IV, IM | 20–40 mg/kg/day, max 2.7 g/day (I) | q8h |
| Clotrimazole,[a] Mycelex | 10-mg lozenge ($) | PO | ≥3 y and adults, dissolve lozenge in mouth (I). | 5 times daily |
| Colistimethate,[a] Coly-Mycin M | 150-mg (colistin base) vial ($$)<br>1-mg base = 2.7-mg colistimethate | IV, IM | 2.5- to 5-mg base/kg/day based on IBW (I)<br>Up to 5- to 7-mg base/kg/day (III) | q8h |
| Cycloserine, Seromycin | 250-mg cap ($$$) | PO | 10–20 mg/kg/day (III)<br>Adults max 1 g/day (I) | q12h |
| Dalbavancin, Dalvance | 500-mg vial ($$$$) | IV | Adults 1 g one time then 500 mg in 1 wk | Once weekly |
| Dapsone[a] | 25-, 100-mg tab ($) | PO | 2 mg/kg, max 100 mg (I) | q24h |
| | | | 4 mg/kg, max 200 mg (I) | Once weekly |
| Daptomycin, Cubicin (Investigational in children <12 y.) | 500-mg vial ($$$$) | IV | 2–5 y: 10 mg/kg (III)<br>≥6–11 y: 7 mg/kg (II)<br>≥12 y and adults: 4–6 mg/kg TBW (I) | q24h |
| Dasabuvir co-packaged with ombitasvir, paritaprevir, ritonavir (ViekiraPak) | Ombitasvir, paritaprevir, ritonavir (12.5-/75-/50-mg) tab + dasabuvir 250-mg tab ($$$$$) | PO | 2 ombitasvir, paritaprevir, ritonavir tabs (each tab [12.5-/75-/50-mg])<br>1 dasabuvir 250-mg tab | qam<br>q12h |
| Demeclocycline,[a] Declomycin | 150-, 300-mg tab ($–$$) | PO | ≥8 y: 7–13 mg/kg/day, max 600 mg/day (I)<br>Dosage differs for SIADH. | q6h |

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Dicloxacillin,[a] Dynapen | 125-, 250-, 500-mg cap ($) | PO | 12–25 mg/kg/day (adults 0.5–1 g/day) (I)<br>For bone and joint infections, up to 100 mg/kg/day, max 2 g/day (III) | q6h |
| Doxycycline,[a] Vibramycin | 25-mg/5-mL susp ($$)<br>50-mg/5-mL syrup ($$)<br>20-, 50-, 75-, 100-mg cap ($)<br>20-, 50-, 75-, 100-mg tab ($) | PO | ≥8 y, ≤45 kg: 2–4 mg/kg/day (I), max 200 mg/day (I) | q12h |
| | 100-mg vial ($$) | IV | | |
| Ertapenem, Invanz | 1-g vial ($$$$) | IV, IM | 30 mg/kg/day, max 1 g/day (I)<br>≥13 y and adults: 1 g/day (I) | q12h<br>q24h |
| Erythromycin base | 250-, 500-mg tab ($$)<br>250-mg cap EC pellets ($$)<br>333-, 500-mg tab EC particle (PCE) ($$$)<br>250-, 333-, 500-mg tab DR (Ery-Tab) ($$) | PO | 50 mg/kg/day, max 4 g/day (I) | q6–8h |
| Erythromycin ethylsuccinate, EES, EryPed | 200-, 400-mg/5-mL susp ($$)<br>400-mg tab ($$) | PO | 50 mg/kg/day, max 4 g/day (I) | q6–8h |
| Erythromycin lactobionate, Erythrocin | 0.5-, 1-g vial ($$$) | IV | 20 mg/kg/day, max 4 g/day (I) | q6h |
| Erythromycin stearate | 250-mg tab ($$) | PO | 50 mg/kg/day, max 4 g/day (I) | q6–8h |
| Ethambutol,[a] Myambutol | 100-, 400-mg tab ($) | PO | 15–25 mg/kg, max 2.5 g (I) | q24h |
| Ethionamide, Trecator | 250-mg tab ($$) | PO | 15–20 mg/kg/day, max 1 g/day (I) | q12–24h |
| Famciclovir,[a] Famvir | 125-, 250-, 500-mg tab ($) | PO | Adults 0.5–1.5 g/day (I) | q8–12h |

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|---|---|---|---|---|
| Fluconazole,[a] Diflucan | 50-, 100-, 150-, 200-mg tab ($)<br>50-, 200-mg/5-mL susp ($) | PO | 6–12 mg/kg/day, max 800 mg/day (I).<br>Max 800–1,000 mg/day may be used for some CNS fungal infections. See Chapter 8. | q24h |
| | 200-, 400-mg vial, IVPB ($–$$) | IV | | |
| Flucytosine,[a] Ancobon | 250-, 500-mg cap ($$$$) | PO | 100 mg/kg/day (I)[b] | q6h |
| Foscarnet, Foscavir | 6-g vial ($$$$) | IV | CMV/VZV: 180 mg/kg/day (I) | q8h |
| | | | CMV suppression: 90–120 mg/kg (I) | q24h |
| | | | HSV: 120 mg/kg/day (I) | q8–12h |
| Ganciclovir,[a] Cytovene | 500-mg vial ($$) | IV | CMV treatment: 10 mg/kg/day (I) | q12h |
| | | | CMV suppression: 5 mg/kg (I) | q24h |
| | | | VZV: 10 mg/kg/day (III) | q12h |
| Gemifloxacin, Factive | 320-mg tab ($$) | PO | Adults 320 mg (I) | q24h |
| Gentamicin[a] | 20-mg/2-mL ($)<br>80-mg/2-mL, 800-mg/20-mL ($) | IV, IM | 3–7.5 mg/kg/day (CF 7–10)[b]; see Chapter 1 regarding q24h dosing. | q8–24h |
| | | Intravesical | 0.5 mg/mL in NS x 50–100 mL (III) | q12h |
| Griseofulvin microsized,[a] Grifulvin V | 125-mg/5-mL susp ($)<br>500-mg tab ($$) | PO | 20–25 mg/kg (II), max 1 g (I) | q24h |
| Griseofulvin ultramicrosized,[a] Gris-PEG | 125-, 250-mg tab ($$) | PO | 10–15 mg/kg (II), max 750 g (I) | q24h |
| Imipenem/cilastatin,[a] Primaxin | 250/250-, 500/500-mg vial ($$) | IV, IM | 60–100 mg/kg/day, max 4 g/day (I)<br>IM form not approved for <12 y | q6h |
| Interferon-PEG<br>Alfa-2a, Pegasys<br>Alfa-2b, PegIntron | Vials, prefilled syringes:<br>135-, 180-µg ($$$$)<br>50-, 80-, 120-, 150-µg ($$$$) | SQ | See Chapter 9, Hepatitis C virus. | Weekly |

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Isavuconazonium (isavuconazole), Cresemba | 186-mg cap (100-mg base) ($$$$)<br>372-mg vial (200-mg base) ($$$$) | PO<br>IV | Adults, 200 mg base per *dose* PO/IV (base = isavuconazole)<br>No pediatric dosing established yet | q8h x 6 doses then q24h |
| Isoniazid,[a] Nydrazid | 50-mg/5-mL syrup ($)<br>100-, 300-mg tab ($)<br>1,000-mg vial ($$) | PO<br>IV, IM | 10–15 mg/kg/day, max 300 mg/day (I) | q12–24h |
| | | | With directly observed biweekly therapy, dosage is 20–30 mg/kg, max 900 mg/dose (I). | Twice weekly |
| Itraconazole, Sporanox | 50-mg/5-mL soln ($$)<br>100-mg cap[a] ($$)<br>200-mg tab ($$$) | PO | 10 mg/kg/day (III), max 200 mg/day | q12h |
| | | | 5 mg/kg/day for chronic mucocutaneous *Candida* (III) | q24h |
| Ivermectin,[a] Stromectol | 3-mg tab ($) | PO | 150–200 µg/kg, no max (I) | 1 dose |
| Ketoconazole,[a] Nizoral | 200-mg tab ($) | PO | ≥2 y: 3.3–6.6 mg/kg, max 400 mg (I) | q24h |
| Levofloxacin,[a] Levaquin | 125-mg/5-mL soln ($)<br>250-, 500-, 750-mg tab ($)<br>500-, 750-mg vial ($)<br>250-, 500-, 750-mg IVPB ($) | PO, IV | For postexposure anthrax prophylaxis (I):<br><50 kg: 16 mg/kg/day, max 500 mg/day<br>≥50 kg: 500 mg q24h<br>For respiratory infections:<br><5 y: 20 mg/kg/day (II)<br>≥5 y: 10 mg/kg/day, max 500 mg/day (II) | <br>q12h<br><br><br>q12h<br>q24h |
| Linezolid, Zyvox | 100-mg/5-mL susp ($$$)<br>600-mg tab[a] ($$$$)<br>200-mg IVPB ($$)<br>600-mg IVPB[a] ($$) | PO, IV | Pneumonia, complicated skin infections, vancomycin-resistant enterococci:<br>Birth–11 y: 30 mg/kg/day (I)<br>>11 y: 1,200 mg/day (I) | <br>q8h<br>q12h |
| | | | Uncomplicated skin infections:<br>Birth–5 y: 30 mg/kg/day (I)<br>5–11 y: 20 mg/kg/day (I)<br>>11–18 y: 1,200 mg/day (I) | <br>q8h<br>q12h<br>q12h |

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|---|---|---|---|---|
| Mefloquine,[a] Lariam | 250-mg tab ($) | PO | See Chapter 10, malaria. | |
| Meropenem,[a] Merrem | 0.5-, 1-g vial ($–$$) | IV | 60 mg/kg/day, max 3 g/day (I)<br>120 mg/kg/day meningitis, max 6 g/day (I) | q8h<br>q8h |
| Methenamine hippurate,[a] Hiprex | 1-g tab ($) | PO | 6–12 y: 1–2 g/day (I)<br>>12 y: 2 g/day (I) | q12h |
| Metronidazole,[a] Flagyl | 250-, 500-mg tab ($)<br>375-mg cap ($) | PO | 30–50 mg/kg/day, max 2,250 mg/day (I) | q8h |
| | 500-mg vial ($)<br>500-mg IVPB ($) | IV | 22.5–40 mg/kg/day (II), max 4 g/day (I) | q6–8h |
| Micafungin, Mycamine | 50-, 100-mg vial ($$$) | IV | 2–4 mg/kg, max 150 mg (I)<br>Neonates 10 mg/kg/day | q24h<br>q24h |
| Miltefosine, Impavido | 50-mg cap<br>Available from CDC | PO | 2.5 mg/kg/day (II) See Chapter 10.<br>≥12 y (I):<br>30–44 kg: 100 mg/day<br>≥45 kg: 150 mg/day | bid<br><br>bid<br>tid |
| Minocycline, Minocin | 50-, 75-, 100-mg cap[a] ($)<br>50-, 75-, 100-mg tab[a] ($)<br>100-mg vial ($$$) | PO, IV | ≥8 y: 4 mg/kg/day, max 200 mg/day (I) | q12h |
| Moxifloxacin, Avelox | 400-mg tab[a]<br>400-mg IVPB | PO, IV | Adults 400 mg/day (I) | q24h |
| Nafcillin,[a] Nallpen | 1-, 2-, 10-g vial ($) | IV, IM | 150–200 mg/kg/day (II)<br>Max 12 g/day div q4h (I) | q6h |
| Neomycin sulfate[a] | 500-mg tab ($) | PO | 50–100 mg/kg/day (II), max 12 g/day (I) | q6–8h |
| Nitazoxanide, Alinia | 100-mg/5-mL susp ($$)<br>500-mg tab ($$$) | PO | 1–3 y: 200 mg/day (I)<br>4–11 y: 400 mg/day (I)<br>≥12 y: 1 g/day (I) | q12h |

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Nitrofurantoin,[a] Furadantin | 25-mg/5-mL susp ($$) | PO | 5–7 mg/kg/day, max 400 mg/day (I) | q6h |
| | | | 1–2 mg/kg for UTI prophylaxis (I) | q24h |
| Nitrofurantoin, macrocrystalline,[a] Macrodantin | 25-, 50-, 100-mg cap ($) | PO | Same as susp | |
| Nitrofurantoin monohydrate and macrocrystalline,[a] Macrobid | 100-mg cap ($) | PO | >12 y: 200 mg/day (I) | q12h |
| Nystatin,[a] Mycostatin | 500,000-U/5-mL susp ($)<br>500,000-U tabs ($) | PO | Infants 2 mL/dose, children 4–6 mL/dose, to coat oral mucosa<br>Tabs: 3–6 tabs/day | q6h<br>tid–qid |
| Oritavancin, Orbactiv | 400-mg vial ($$$$) | IV | Adults 1,200 mg/day (I) | One time |
| Oseltamivir, Tamiflu (See Chapter 9, Influenza virus.) | 30-mg/5-mL susp ($$)<br>30-, 45-, 75-mg cap ($$) | PO | Preterm, <38 wk PMA (II):<br>1 mg/kg/dose PO bid<br>Preterm, 38–40 wk PMA (II):<br>1.5 mg/kg/dose PO bid<br>Preterm, >40 wk PMA (II), and term, birth–8 mo (I):<br>3 mg/kg/dose PO bid<br>9–11 mo (II):<br>3.5 mg/kg/dose PO bid<br>≥12 mo (I):<br>≤15 kg: 60 mg/day<br>>15–23 kg: 90 mg/day<br>>23–40 kg: 120 mg/day<br>>40 kg: 150 mg/day | q12h |

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| | | | Prophylaxis: Give at the same mg/kg dose but qd rather than bid. Not recommended for infants <3 mo. | q24h |
| Oxacillin,[a] Bactocill | 1-, 2-, 10-g vial ($$) | IV, IM | 100 mg/kg/day, max 12 g/day (I)<br>150–200 mg/kg/day for meningitis (III) | q4–6h |
| Palivizumab, Synagis | 50-, 100-mg vial ($$$$) | IM | 15 mg/kg (I) | Monthly |
| Paromomycin,[a] Humatin | 250-mg cap ($) | PO | 25–35 mg/kg/day, max 4 g/day (I) | q8h |
| Penicillin G intramuscular | | | | |
| – Penicillin G benzathine, Bicillin L-A | 600,000 U/mL in 1-, 2-, 4-mL prefilled syringes ($–$$) | IM | 50,000 U/kg for newborns and infants, children <60 lb: 300,000–600,000 U, children ≥60 lb: 900,000 U (I)<br>(FDA approved in 1952 for dosing by pounds) | 1 dose for treatment |
| – Penicillin G benzathine/procaine, Bicillin C-R, Bicillin C-R pediatric | 1,200,000 IU per 2 mL prefilled syringe as 600,000 IU benzathine + 600,000 IU procaine per mL ($).<br>Pediatric has a 1-inch needle. | IM | <30 lb: 600,000 U<br>30–60 lb: 900,000–1,200,000 U<br>>60 lb: 2,400,000 U (I) | 1 dose usually (may need repeat injections q2–3d) |
| – Penicillin G procaine[a] | 600,000 U/mL in 1-, 2-mL prefilled syringes ($$) | IM | 50,000 U/kg/day, max 1,200,000 U per dose (I) | q12–24h |
| Penicillin G intravenous | | | | |
| – Penicillin G K,[a] Pfizerpen | 5-, 20-million unit vial ($) | IV, IM | 100,000–300,000 units/kg/day (I).<br>Max daily dose is 24 million units. | q4–6h |
| – Penicillin G sodium[a] | 5-million unit vial ($$) | IV, IM | 100,000–300,000 unit/kg/day (I).<br>Max daily dose is 24 million units. | q4–6h |
| Penicillin V oral | | | | |
| – Penicillin V K[a] | 125-, 250-mg/5-mL soln ($)<br>250-, 500-mg tab ($) | PO | 25–50 mg/kg/day, max 2 g/day (I) | q6h |

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Pentamidine,[a] Pentam Nebupent | 300-mg vial ($$$) | IV, IM | 4 mg/kg/day (I), max 300 mg | q24h |
| | 300-mg vial ($$) | Inhaled | 300 mg monthly for prophylaxis (I) | q24h |
| Peramivir, Rapivab | 200-mg vial ($$$) | IV | 10 mg/kg (II), max 600 mg (I) | One time |
| Piperacillin/tazobactam,[a] Zosyn | 2/0.25-, 3/0.375-, 4/0.5-, 36/4.5-g vial ($) | IV | ≤40 kg: 240–300 mg PIP/kg/day, max 16 g PIP/day (I) | q8h |
| Polymyxin B[a] | 500,000 U vial ($)<br>1 mg = 10,000 U | IV | 2.5 mg/kg/day (I)<br>Adults 2 mg/kg LD, then 2.5–3 mg/kg/day, dose based on TBW, no max (II) | q12h |
| Posaconazole, Noxafil (See Chapter 8.) | 200-mg/5-mL susp ($$$$) | PO | <13 y:<br>Under investigation, 18 mg/kg/day with serum trough monitoring. | q8h |
| | | | ≥13 y and adults (I):<br>Oropharyngeal candidiasis:<br>100 mg q12h for 1 day, then 100 mg/day<br>800 mg/day for refractory disease<br>Prophylaxis of invasive *Aspergillus* or *Candida*:<br>600 mg/day | <br><br>q24h<br>q12h<br>q8h |
| | 100-mg DR tab ($$$$)<br>300-mg/16.7-mL vial ($$$$) | PO<br>IV | ≥13 y and adults (I):<br>Prophylaxis of invasive *Aspergillus* or *Candida*:<br>300 mg q12h for 1 day, then 300 mg/day<br>Pediatric dosing unknown | q24h |
| Praziquantel, Biltricide | 600-mg tri-scored tab ($$) | PO | 20–25 mg/kg, no max (I) | q4–6h for 3 doses |
| Primaquine phosphate[a] | 15-mg base tab ($) | PO | 0.3 mg base/kg, max 30 mg (III)<br>(See also Chapter 10.)<br>(26.3-mg primaquine phosphate = 15-mg base) | q24h |

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|---|---|---|---|---|
| Pyrantel pamoate,[a] Pin-X | 250-mg base chew tab ($)<br>250-mg base/5-mL susp ($) | PO | 11 mg (base)/kg, max 1 g (I)<br>(144-mg pyrantel pamoate = 50-mg base) | Once |
| Pyrazinamide[a] | 500-mg tab ($) | PO | 30 mg/kg/day, max 2 g/day (I) | q24h |
| | | | Directly observed biweekly therapy, 50 mg/kg (I) use IBW, no max. | Twice weekly |
| Quinupristin/dalfopristin, Synercid | 150/350-mg vial (500 mg total) ($$$$) | IV | 22.5 mg/kg/day (II)<br>Adults 15–22.5 mg/kg/day, no max (I) | q8h<br>q8–12h |
| Raxibacumab | 1,700-mg/35-mL vial<br>Available from CDC | IV | ≤15 kg: 80 mg/kg<br>15–50 kg: 60 mg/kg<br>>50 kg: 40 mg/kg (I) | Once |
| Ribavirin, Rebetol (See Chapter 9.) | 200-mg cap/tab[a] ($)<br>600-mg dose pak[a] ($$$)<br>200-mg/5-mL soln ($$$) | PO | 15 mg/kg/day (with interferon) (II) | q12h |
| Ribavirin, Virazole | 6-g vial ($$$$$) | Inhaled | 1 vial by SPAG-2; see Chapter 9, RSV. | q24h |
| Rifabutin,[a] Mycobutin | 150-mg cap ($$–$$$) | PO | 5 mg/kg for MAC prophylaxis (II)<br>10–20 mg/kg for MAC or TB treatment (I)<br>Max 300 mg/day | q24h |
| Rifampin,[a] Rifadin | 150-, 300-mg cap ($)<br>600-mg vial ($$$) | PO, IV | 10–20 mg/kg, max 600 mg for TB (I) | q24h |
| | | | With directly observed biweekly therapy, dosage is still 10–20 mg/kg/dose (max 600 mg). | Twice weekly |
| | | | 20 mg/kg/day for 2 days for meningococcus prophylaxis, max 1.2 g/day (I) | q12h |
| Rifampin/isoniazid/ pyrazinamide, Rifater | 120-/50-/300-mg tab ($$$) | PO | ≥15 y and adults:<br>≤44 kg: 4 tab<br>45–54 kg: 5 tab<br>≥55 kg: 6 tab | q24h |

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Rifapentine, Priftin | 150-mg tab ($$) | PO | ≥12 y and adults: 600 mg/dose (I) | Twice weekly |
| Rifaximin, Xifaxan | 200-mg tab ($$) | PO | ≥12 y and adults: 600 mg/day (I) | q8h |
| Simeprevir, Olysio | 150-mg cap ($$$$$) | PO | Adults 150 mg[c] (I) | q24h |
| Sofosbuvir, Sovaldi | 400-mg tab ($$$$$) | PO | Adults 400 mg[c] (I) | q24h |
| Sofosbuvir/Ledipasvir, Harvoni | 400-/90-mg tab ($$$$$) | PO | Adults 1 tab (I) | q24h |
| Streptomycin[a] | 1-g vial ($$) | IM, IV | 20–40 mg/kg/day, max 1 g/day[b] (I) | q12–24h |
| Sulfadiazine[a] | 500-mg tab ($–$$) | PO | 120–150 mg/kg/day, max 4–6 g/day (I) | q6h |
| | | | Rheumatic fever secondary prophylaxis 500 mg once daily if ≤27 kg, 1,000 mg once daily if >27 kg (II) | q24h |
| | | | See also Chapter 10. | |
| Tedizolid, Sivextro | 200-mg tab ($$$$)<br>200-mg vial ($$$$) | PO, IV | Adults 200 mg (I) | q24h |
| Telavancin, Vibativ | 250-, 750-mg vial ($$$$) | IV | Adults 10 mg/kg | q24h |
| Telbivudine, Tyzeka | 600-mg tab ($$$$) | PO | ≥16 y and adults 600 mg/day (I) | q24h |
| Telithromycin, Ketek | 300-, 400-mg tab ($$) | PO | Adults 800 mg/day (I) | q24h |
| Terbinafine, Lamisil | 125-, 187.5-mg granules ($$$)<br>250-mg tab[a] ($) | PO | >4 y<br><25 kg: 125 mg/day<br>25–35 kg: 187.5 mg/day<br>>35 kg: 250 mg/day (I) | q24h |
| Tetracycline[a] | 250-, 500-mg cap ($$) | PO | ≥8 y: 25–50 mg/kg/day (I) | q6h |

| | | | | |
|---|---|---|---|---|
| Ticarcillin/clavulanate, Timentin | 30-/1-g vial ($$) | IV | 200–300 mg ticarcillin/kg/day, max 18 g/day (I) | q4–6h |
| Tinidazole,[a] Tindamax | 250-, 500-mg tab ($) | PO | 50 mg/kg, max 2 g (I)<br>See also Chapter 10. | q24h |
| Tobramycin,[a] Nebcin | 20-mg/2-mL vial ($)<br>40-mg/mL 2-, 30-, 50-mL vial ($) | IV, IM | 3–7.5 mg/kg/day (CF 7–10)[b]; see Chapter 1 regarding q24h dosing. | q8–24h |
| Tobramycin inhalation,[a] Tobi | 300-mg ampule ($$$$) | Inhaled | ≥6 y: 600 mg/day (I) | q12h |
| Tobi Podhaler | 28-mg cap for inhalation ($$$$) | Inhaled | ≥6 y: 224 mg/day via Podhaler device (I) | q12h |
| Trimethoprim/sulfamethoxazole,[a] Bactrim, Septra | 80-mg TMP/400-mg SMX tab (single strength) ($)<br>160-mg TMP/800-mg SMX tab (double strength) ($)<br>40-mg TMP/200-mg SMX per 5-mL susp ($)<br>16-mg TMP/80-mg SMX per mL inject soln in 5-, 10-, 30-mL vial ($) | PO, IV | 8–10 mg TMP/kg/day (I) | q12h |
| | | | 2 mg TMP/kg/day for UTI prophylaxis (I) | q24h |
| | | | 15–20 mg TMP/kg/day for PCP treatment (I), no max | q6–8h |
| | | | 150 mg TMP/$m^2$/day, OR 5 mg TMP/kg/day for PCP prophylaxis (I), max 160 mg TMP/day | q12h 3 times a week OR q24h |
| Valacyclovir,[a] Valtrex | 500-mg, 1-g tab ($) | PO | VZV: ≥3 mo: 60 mg/kg/day (I, II)<br>HSV: ≥3 mo: 40 mg/kg/day (II)<br>Max single dose 1 g (I) | q8h<br>q12h |
| Valganciclovir, Valcyte | 250-mg/5-mL soln ($$$–$$$$)<br>450-mg tab ($$$$) | PO | Congenital CMV treatment: 32 mg/kg/day (II).<br>CMV prophylaxis: 7 x BSA x CrCl (using the modified Schwartz formula for CrCl), max 900 mg (I).<br>See also Chapter 9. | q12h<br>q24h |

## A. SYSTEMIC ANTIMICROBIALS WITH DOSAGE FORMS AND USUAL DOSAGES (continued)

| Generic and Trade Names | Dosage Form (cost estimate) | Route | Dose (evidence level) | Interval |
|---|---|---|---|---|
| Vancomycin,[a] Vancocin | 125-, 250-mg/5-mL susp ($)<br>125-, 250-mg cap ($$–$$$) | PO | 40 mg/kg/day (I), max 500 mg/day (III) | q6h |
| | 0.5-, 0.75-, 1-, 5-, 10-g vial ($) | IV | 30–40 mg/kg/day[a] (I)<br>For life-threatening invasive MRSA infection, 60–70 mg/kg/day adjusted to achieve an AUC:MIC of >400 mg/L × h (II) | q6–8h |
| Voriconazole,[a] Vfend (See Chapter 8.) | 200-mg/5-mL susp ($$$)<br>50-, 200-mg tab ($–$$) | PO | 2–12 y: 18 mg/kg/day (II)<br>>12 y: 400 mg/day (I) | q12h |
| | 200-mg vial ($$$) | IV | 2–12 y: 18 mg/kg/day LD for 1 day, then 16 mg/kg/day (II)<br>>12 y: 12 mg/kg/day LD for 1 day, then 8 mg/kg/day (max 600 mg/day) (I) | q12h |
| Zanamivir, Relenza | 5-mg blister cap for inhalation ($$) | Inhaled | Prophylaxis: ≥5 y: 10 mg (I) | q24h |
| | | | Treatment: ≥7 y: 10 mg (I) | q12h |

[a] Available in a generic formulation.

[b] Monitor serum concentrations.

[c] Given as a cocktail with ribavirin ± interferon-PEG.

## B. TOPICAL ANTIMICROBIALS (SKIN, EYE, EAR)

| Generic and Trade Names | Dosage Form | Route | Dose | Interval |
|---|---|---|---|---|
| Azithromycin, AzaSite | 1% ophth soln | Ophth | 1 drop | bid for 2 days then qd for 5 days |
| Bacitracin[a] | Ophth oint | Ophth | Apply to affected eye. | q3–4h |
| | Oint[b] | Top | Apply to affected area. | bid–qid |
| Benzyl alcohol, Ulesfia | 5% lotion | Top | Apply to scalp and hair. | Once; repeat in 7 days. |
| Besifloxacin, Besivance | 0.6% ophth susp | Ophth | ≥1 y: 1 drop to affected eye | tid |
| Butenafine, Mentax | 1% cream | Top | ≥12 y: apply to affected area. | qd |
| Butoconazole, Gynazole-1 | 2% prefilled cream | Vag | Adults 1 applicatorful | One time |
| Ciclopirox,[b] Loprox, Penlac | 0.77% cream, gel, lotion | Top | ≥10 y: apply to affected area. | bid |
| | 1% shampoo | | ≥16 y: apply to scalp. | Twice weekly |
| | 8% nail lacquer | | ≥12 y: apply to infected nail. | qd |
| Ciprofloxacin,[a] Cetraxal | 0.2% otic soln | Otic | ≥1 y: apply 3 drops to affected ear. | bid for 7 days |
| Ciprofloxacin,[a] Ciloxan | 0.3% ophth soln | Ophth | ≥12 y: apply to affected eye. | q2h for 2 days then q4h for 5 days |
| | 0.3% ophth oint | | | q8h for 2 days then q12h for 5 days |
| Ciprofloxacin + dexamethasone, Ciprodex | 0.3% + 0.1% otic soln | Otic | ≥6 mo: apply 4 drops to affected ear. | bid for 7 days |

## B. TOPICAL ANTIMICROBIALS (SKIN, EYE, EAR) (continued)

| Generic and Trade Names | Dosage Form | Route | Dose | Interval |
|---|---|---|---|---|
| Ciprofloxacin + hydrocortisone, Cipro HC | 0.2% + 1% otic soln | Otic | ≥1 y: apply 3 drops to affected ear. | bid for 7 days |
| Clindamycin | | | | |
| Clindesse | 2% cream | Vag | Adolescents and adults 1 applicatorful | One time |
| Cleocin | 100-mg ovule | | 1 ovule | qhs for 3 days |
| | 2% cream[a] | | 1 applicatorful | qhs for 3–7 days |
| Cleocin-T[a] | 1% soln, gel, lotion | Top | Apply to affected area. | qd–bid |
| Evoclin | 1% foam | | | qd |
| Clindamycin + benzoyl peroxide,[a] BenzaClin | 1% gel | Top | ≥12 y: apply to affected area. | bid |
| Acanya | 1.2% gel | Top | Apply small amount to face. | q24h |
| Clindamycin + tretinoin, Ziana, Veltin | 1.2% gel | Top | Apply small amount to face. | hs |
| Clotrimazole,[a,b] Lotrimin | 1% cream, lotion, soln | Top | Apply to affected area. | bid |
| Gyne-Lotrimin-7[a,b] | 1% cream | Vag | ≥12 y: 1 applicatorful | qhs for 7–14 days |
| Gyne-Lotrimin-3[a,b] | 2% cream | | | qhs for 3 days |
| Clotrimazole + betamethasone,[a] Lotrisone | 1% + 0.05% cream, lotion | Top | ≥12 y: apply to affected area. | bid |
| Colistin + neomycin + hydrocortisone, Coly-Mycin S, Cortisporin TC otic | 0.3% otic susp | Otic | Apply 3–4 drops to affected ear canal; may use with wick. | q6–8h |
| Cortisporin; bacitracin + neomycin + polymyxin B + hydrocortisone | Oint | Top | Apply to affected area. | bid–qid |

| | | | | |
|---|---|---|---|---|
| Cortisporin; neomycin + polymyxin B + hydrocortisone | Otic soln,[a] susp | Otic | 3 drops to affected ear | bid–qid |
| | Cream | Top | Apply to affected area. | bid–qid |
| Dapsone, Aczone | 5% gel | Top | Apply to affected area. | bid |
| Econazole,[a] Spectazole | 1% cream | Top | Apply to affected area. | qd–bid |
| Efinaconazole, Jublia | 10% soln | Top | Apply to toenail. | qd for 48 wk |
| Erythromycin | 0.5% ophth oint[a] | Ophth | Apply to affected eye. | q4h |
| Eryderm, Erygel | 2% soln,[a] gel[a] | Top | Apply to affected area. | bid |
| Ery Pads | 2% pledgets[a] | | | |
| Akne-Mycin | 2% oint | | | |
| Erythromycin + benzoyl peroxide,[a] Benzamycin | 3% gel | Top | ≥12 y: apply to affected area. | qd–bid |
| Finafloxacin, Xtoro | 0.3% otic susp | Otic | >1 y: 4 drops in affected ear | bid for 7 days |
| Ganciclovir, Zirgan | 0.15% ophth gel | Ophth | ≥2 y: 1 drop in affected eye | q3h while awake (5 times/day) until healed then tid for 7 days |
| Gatifloxacin, Zymaxid | 0.5% ophth soln | Ophth | Apply to affected eye. | q2h for 1 day then q6h |
| Gentamicin,[a] Garamycin | 0.1% cream, oint | Top | Apply to affected area. | tid–qid |
| | 0.3% ophth soln, oint | Ophth | Apply to affected eye. | q1–4h (soln)<br>q4–8h (oint) |
| Gentamicin + prednisolone, Pred-G | 0.3% ophth soln, oint | Ophth | Adults: apply to affected eye. | q1–4h (soln) |
| | | | | qd–tid (oint) |

## B. TOPICAL ANTIMICROBIALS (SKIN, EYE, EAR) (continued)

| Generic and Trade Names | Dosage Form | Route | Dose | Interval |
|---|---|---|---|---|
| Ivermectin, Sklice | 0.5% lotion | Top | ≥6 mo: thoroughly coat hair and scalp, rinse after 10 minutes. | Once |
| Ketoconazole | | Top | ≥12 y: apply to affected area. | |
| Nizoral | 2% shampoo[a] | | | qd |
| | 2% cream[a] | | | qd–bid |
| Nizoral A-D[a] | 1% shampoo | | | bid |
| Extina, Xolegel | 2% foam,[a] gel | | | bid |
| Levofloxacin,[a] Quixin | 0.5% ophth soln | Ophth | Apply to affected eye. | q1–4h |
| Luliconazole, Luzu | 1% cream | Top | Adults: apply to affected area. | q24h for 1–2 wk |
| Mafenide, Sulfamylon | 8.5% cream | Top | Apply to burn. | qd–bid |
| | 5-g pwd for reconstitution | | To keep burn dressing wet | q4–8h as needed |
| Malathion, Ovide | 0.5% soln | Top | ≥6 y: apply to hair and scalp. | Once |
| Maxitrol[a]; neomycin + polymyxin B + dexamethasone | Susp, oint | Ophth | Apply to affected eye. | q4h (oint)<br>q1–4h (susp) |
| Metronidazole[a] | 0.75% cream, gel, lotion | Top | Adults: apply to affected area. | bid |
| MetroGel-Vaginal[a] | 0.75% vag gel | Vag | Adults 1 applicatorful | qd–bid |
| Noritate, MetroGel | 1% cream, gel | Top | Adults: apply to affected area. | qd |
| Miconazole | | | | |
| Micatin[a,b] and others | 2% cream, pwd, oint, spray, lotion, gel | Top | Apply to affected area. | qd–bid |

| | | | | |
|---|---|---|---|---|
| Fungoid[a] | 2% tincture | Top | Apply to affected area. | bid |
| Vusion | 0.25% oint | Top | To diaper dermatitis | Each diaper change for 7 days |
| Monistat-1[a,b] | 1.2-g ovule + 2% cream | Vag | ≥12 y: insert one ovule (plus cream to external vulva bid as needed). | Once |
| Monistat-3[a,b] | 200-mg ovule, 4% cream | | | qhs for 3 days |
| Monistat-7[a,b] | 100-mg ovule, 2% cream | | | qhs for 7 days |
| Moxifloxacin, Vigamox | 0.5% ophth soln | Ophth | Apply to affected eye. | tid |
| Mupirocin, Bactroban | 2% oint,[a] cream,[a] nasal oint | Top | Apply to infected skin or nasal mucosa. | tid |
| Naftifine, Naftin | 2% cream, gel | Top | Adults: apply to affected area. | qd |
| Natamycin, Natacyn | 5% ophth soln | Ophth | Adults: apply to affected eye. | q1–4h |
| Neosporin[a] | | | | |
| bacitracin + neomycin | Ophth oint | Ophth | Apply to affected eye. | q4h |
| + polymyxin B | Top oint[a] | Top | Apply to affected area. | bid–qid |
| gramicidin + neomycin + polymyxin B | Ophth soln | Ophth | Apply to affected eye. | q4h |
| Nystatin,[a] Mycostatin | 100,000 U/g cream, oint, pwd | Top | Apply to affected area. | bid–qid |
| Nystatin + triamcinolone,[a] Mycolog II | 100,000 U/g + 0.1% cream, oint | Top | Apply to affected area. | bid |
| Ofloxacin,[a] Floxin Otic | 0.3% otic soln | Otic | 5–10 drops to affected ear | qd–bid |
| Ocuflox | 0.3% ophth soln | Ophth | Apply to affected eye. | q1–6h |
| Oxiconazole, Oxistat | 1% cream, lotion | Top | Apply to affected area. | qd–bid |

## B. TOPICAL ANTIMICROBIALS (SKIN, EYE, EAR) (continued)

| Generic and Trade Names | Dosage Form | Route | Dose | Interval |
|---|---|---|---|---|
| Permethrin, Nix[a,b] | 1% cream | Top | Apply to hair/scalp. | Once for 10 min |
| Elimite[a] | 5% cream | | Apply to all skin surfaces. | Once for 8–14 h |
| Piperonyl butoxide + pyrethrins,[a,b] Rid | 4% + 0.3% shampoo, gel | Top | Apply to affected area. | Once for 10 min |
| Polysporin,[a] polymyxin B + bacitracin | Ophth oint | Ophth | Apply to affected eye. | qd–tid |
| | Oint[a] | Top | Apply to affected area. | qd–tid |
| Polytrim,[a] polymyxin B + trimethoprim | Ophth soln | Ophth | Apply to affected eye. | q3–4h |
| Retapamulin, Altabax | 1% oint | Top | Apply thin layer to affected area. | bid for 5 days |
| Selenium sulfide,[a] Selsun | 2.5% susp/lotion | Top | Lather into scalp or affected area. | Twice weekly then every 1–2 wk |
| Selsun Blue[a,b] | 1% shampoo | Top | | qd |
| Sertaconazole, Ertaczo | 2% cream | Top | ≥12 y: apply to affected area. | bid |
| Silver sulfadiazine,[a] Silvadene | 1% cream | Top | Apply to affected area. | qd–bid |
| Spinosad, Natroba | 0.9% susp | Top | Apply to scalp and hair. | Once; may repeat in 7 days. |
| Sulconazole, Exelderm | 1% soln, cream | Top | Adults: apply to affected area. | qd–bid |
| Sulfacetamide sodium[a] | 10%, 15%, 30% soln | Ophth | Apply to affected eye. | q1–3h |
| | 10% ophth oint | | | q4-6h |
| | 10% top lotion | Top | ≥12 y: apply to affected area. | bid–qid |
| Sulfacetamide sodium + fluorometholone, FML-S | 10% ophth soln | Ophth | Apply to affected eye. | qid |

| | | | | |
|---|---|---|---|---|
| Sulfacetamide sodium + prednisolone, Blephamide | 10% ophth oint, soln | Ophth | Apply to affected eye. | tid–qid |
| Tavaborole, Kerydin | 5% soln | Top | Adults: apply to toenail. | qd for 48 wk |
| Terbinafine, Lamisil-AT[b] | 1% cream, spray, gel | Top | Apply to affected area. | qd–bid |
| Terconazole,[a] Terazol-7 | 0.4% cream | Vag | Adults 1 applicatorful or 1 supp | qhs for 7 days |
| Terazol-3 | 0.8% cream, 80 mg supp | | | qhs for 3 days |
| Tioconazole[a,b] | 6.5% ointment | Vag | ≥12 y 1 applicatorful | One time |
| Tobramycin,[a] Tobrex | 0.3% ophth soln, oint | Ophth | Apply to affected eye. | q1–4h (soln)<br>q4–8h (oint) |
| Tobramycin + dexamethasone, Tobradex | 0.3% ophth soln,[a] oint | Ophth | Apply to affected eye. | q2–6h (soln)<br>q6–8h (oint) |
| Tolnaftate,[a,b] Tinactin | 1% cream, soln, pwd, spray | Top | Apply to affected area. | bid |
| Trifluridine,[a] Viroptic | 1% ophth soln | Ophth | 1 drop (max 9 drops/day) | q2h |

[a] Generic available.
[b] Over the counter.

## 12. Antibiotic Therapy for Children Who Are Obese

When prescribing an antimicrobial for a child who is obese, selecting a dose based on mg per kg of total body weight (TBW) may expose the child to supratherapeutic plasma concentrations if the drug doesn't freely distribute into fat tissue. The aminoglycosides and beta-lactams are examples of such potentially problematic antibiotics because they are hydrophilic molecules and their distribution volumes are correlated with extracellular fluid. In general, these and other hydrophilic compounds may be dosed using a weight adjustment of 30% to 50% of the difference between TBW and expected body weight (EBW); see the following Dosing Recommendations table.

For **aminoglycosides** in obese adults and children, a 40% adjustment in dosing weight has been recommended. When performing this empiric dosing with aminoglycosides in children who are obese, we recommend closely following serum concentrations.

**Vancomycin** is traditionally dosed based on TBW in obese adults due to increases in kidney size and glomerular filtration rate. In children who are obese, TBW-based dosing may result in supratherapeutic concentrations. Dosing adjustments using body surface area may be more appropriate. As with aminoglycosides, we recommend early and frequent serum measurement to confirm dosing predictions.

In the setting of **cephalosporins** for surgical prophylaxis (see Chapter 14), adult studies of obese patients have generally found that distribution to the subcutaneous fat tissue target is subtherapeutic when standard doses are used. Given the wide safety margin of these agents in the short-term setting of surgical prophylaxis, maximum single doses are recommended in obese adults (eg, cefazolin 2–3 g instead of the standard 1 g) with re-dosing at 4-hour intervals for longer cases. Based on the adult data, we recommend dosing cephalosporins for surgical prophylaxis based on TBW up to the adult maximum.

In critically ill obese adults, extended infusion times have been shown to increase the likelihood of achieving therapeutic serum concentrations with **carbapenems** and antipseudomonal **penicillins**.

Monitor creatine kinase when using **daptomycin** in a child who is obese.

Listed in the Table are the major classes of antimicrobials and our suggestion on how to calculate the most appropriate dose. The levels of evidence to support these recommendations are Level II–III (pharmacokinetic studies in children, extrapolations from adult studies, and expert opinion). Whenever a dose is used that is greater than one prospectively investigated for efficacy and safety, the clinician must weigh the benefits with potential risks. Data are not available on all agents.

| | DOSING RECOMMENDATIONS | | |
|---|---|---|---|
| **Drug Class** | **By EBW[a]** | **Intermediate Dosing** | **By TBW[b]** |
| **ANTIBACTERIALS** | | | |
| **Beta-lactams** | | **EBW + 0.5 (TBW-EBW)** | |
| Penicillins | | X | |
| Cephalosporins | | X | X (surgical prophylaxis) |
| Carbapenems | | X | |
| **Macrolides** | | | |
| Erythromycin | X | | |
| Azithromycin | X (for gastrointestinal infections) | | X |
| Clarithromycin | X | | |
| **Lincosamides** | | | |
| Clindamycin | | | X |
| **Glycopeptides** | | | |
| Vancomycin | | 1,500–2,000 mg/m$^2$/d | X |
| **Aminoglycosides** | | **EBW + 0.4 (TBW-EBW)** | |
| Gentamicin | | X | |
| Tobramycin | | X | |
| Amikacin | | X | |
| **Fluoroquinolones** | | **EBW + 0.45 (TBW-EBW)** | |
| Ciprofloxacin | | X | |
| Levofloxacin | | X | |
| **Rifamycins** | | | |
| Rifampin | X | | |
| **Miscellaneous** | | | |
| TMP/SMX | | | X |
| Metronidazole | X | | |
| Linezolid | X | | |
| Daptomycin | | | X |

| | DOSING RECOMMENDATIONS | | |
|---|---|---|---|
| **Drug Class** | **By EBW[a]** | **Intermediate Dosing** | **By TBW[b]** |
| **ANTIFUNGALS** | | | |
| **Polyenes** | | | |
| Amphotericin B (conventional and lipid formulations) | | | X |
| **Azoles** | | | |
| Fluconazole | | | X |
| Voriconazole | X | | |
| **Pyrimidine Analogues** | | | |
| Flucytosine | X | | |
| **Echinocandins** | | | |
| Caspofungin | | | X |
| Micafungin | | X | |
| **ANTIVIRALS (NON-HIV)** | | | |
| Nucleoside analogues (acyclovir, ganciclovir) | X | | |
| Oseltamivir | X | | |
| **ANTIMYCOBACTERIALS** | | | |
| Isoniazid | X | | |
| Rifampin | X | | |
| Pyrazinamide | X | | |
| Ethambutol | X | | |

Abbreviations: BMI, body mass index; EBW, expected body weight; HIV, human immunodeficiency virus; TBW, total body weight; TMP/SMX, trimethoprim/sulfamethoxazole.

[a] EBW (kg) = BMI 50th percentile for age × actual height $(m)^2$; from Le Grange D, et al. *Pediatrics.* 2012;129:e438–e446.

[b] Actual measured body weight.



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Smith M, et al. *E-PAS.* 2015:4194.689

## 13. Sequential Parenteral-Oral Antibiotic Therapy (Oral Step-down Therapy) for Serious Infections

Bacterial pneumonias, bone and joint infections,[1–3] deep-tissue abscesses, and appendicitis,[4,5] as well as cellulitis or pyelonephritis,[6] may require initial parenteral therapy to control the growth and spread of pathogens and minimize injury to tissues. However, intravenous (IV) therapy carries risks of catheter-related complications that are unpleasant for the child whether therapy is provided in the hospital or on an outpatient basis. For the beta-lactam class of antibiotics, absorption of orally administered antibiotics in standard dosages provides peak serum concentrations that are routinely only 5% to 20% of those achieved with IV or intramuscular administration. However, clindamycin and many newer antibiotics of the fluoroquinolone class (ciprofloxacin, levofloxacin)[7] and oxazolidinone class (linezolid, tedizolid) have excellent absorption of their oral formulations and provide virtually the same tissue antibiotic exposure at a particular mg/kg dose, compared with the exposure when the antibiotic is given at that dose IV. Following initial parenteral therapy of serious infections, it may be possible to provide oral antibiotic therapy to achieve the tissue antibiotic exposure that is required for cure. One must also assume that the parent and child are compliant with the administration of each antibiotic dose and that the parents will seek medical care if the clinical course does not continue to improve for their child.

High-dose oral beta-lactam antibiotic therapy of osteoarticular infections, associated with achieving a particular level of bactericidal activity in serum, has been associated with treatment success since 1978.[7] It is reassuring that high-quality retrospective cohort data have recently confirmed the similar outcomes achieved in those treated with oral step-down therapy compared with those treated with IV.[8] While most hospital laboratories no longer offer bactericidal assays, the need to achieve bactericidal activity with high-dose oral therapy, explained later in this chapter, remains important. Comparable mg/kg dosages of parenteral and oral beta-lactam medications often result in comparable tissue concentrations 4 to 6 hours after a dose (although the high mg/kg doses given orally may not always be well tolerated). The momentary high serum concentrations that occur during IV administration of beta-lactam antibiotics may provide for better tissue penetration; however, killing of bacteria by beta-lactam antibiotics is not dependent on the height of the antibiotic concentration but on the time that the antibiotic is present at the site of infection at concentrations above the minimum inhibitory concentration of the antibiotic for that pathogen.

For abscesses in soft tissues, joints, and bones, most organisms are removed by surgical drainage and presumably killed by the initial parenteral therapy. When the signs and symptoms of infection begin to resolve, usually within 1 to 4 days, continuing IV therapy may not be required, as a normal host response neutrophil begins to assist in clearing the infection. Following objective laboratory markers such as C-reactive protein (CRP) or procalcitonin (PCT) during the hospitalization may help the clinician better assess the response to therapy, particularly in the infant or child who is difficult to examine.[9,10]

High-dosage oral beta-lactam therapy (based on in vitro susceptibilities) provides the tissue antibiotic exposure required to eradicate the remaining pathogens at the infection site as the tissue perfusion improves. For beta-lactams, begin with a dosage 2 to 3 times the normal dosage (eg, 75–100 mg/kg/day of amoxicillin or 100 mg/kg/day of cephalexin). High-dose prolonged oral beta-lactam therapy may be associated with reversible neutropenia; checking for hematologic toxicity every few weeks during therapy should be considered. For deep methicillin-resistant *Staphylococcus aureus* infections, oral step-down therapy with clindamycin or linezolid is recommended.[11]

Monitor the child clinically for a continued response on oral therapy; follow CRP or PCT after the switch to oral therapy if there are concerns about continued response to make sure that the antibiotic and dosage you selected are appropriate.

## 14. Antimicrobial Prophylaxis/Prevention of Symptomatic Infection

This chapter provides a summary of recommendations for prophylaxis of infections, defined as providing therapy prior to the onset of clinical signs or symptoms of infection. Prophylaxis can be considered in several clinical scenarios.

**A. Postexposure Short-term Antimicrobial Prophylaxis**
Given for a short, specified period after exposure to specific pathogens/organisms, where the risks of acquiring the infection are felt to justify antimicrobial treatment to eradicate the pathogen or prevent symptomatic infection in situations in which the child (healthy or with increased susceptibility to infection) is likely to have been inoculated (eg, asymptomatic child closely exposed to meningococcus; a neonate born to a mother with active genital herpes simplex virus).

**B. Long-term Antimicrobial Prophylaxis to Prevent Symptomatic Disease**
Given to a particular, defined population of children who are of relatively high risk of acquiring a severe infection (eg, a child post-splenectomy; a child with documented rheumatic heart disease to prevent subsequent streptococcal infection), with prophylaxis provided during the period of risk, potentially months or years.

**C. Preemptive Treatment/Latent Infection Treatment ("Prophylaxis of Symptomatic Disease in Children Who Have Asymptomatic Infection")**
Where a child has a documented but asymptomatic infection and targeted antimicrobials are given to prevent the development of symptomatic disease (eg, latent tuberculosis infection or therapy of a stem cell transplant patient with documented cytomegalovirus viremia but no symptoms of infection or rejection). Treatment period is usually defined, but certain circumstances, such as reactivation of a herpesvirus, may require re-treatment.

**D. Surgical/Procedure Prophylaxis**
A child receives a surgical/invasive catheter procedure, planned or unplanned, where the risk of infection postoperatively or post-procedure may justify prophylaxis to prevent an infection from occurring (eg, prophylaxis to prevent infection following spinal rod placement). Treatment is usually short-term, beginning just prior to the procedure and ending at the conclusion of the procedure, or within 24 to 48 hours.

**E. Travel-Related Exposure Prophylaxis**
Not discussed in this chapter; please refer to information on specific disease entities (eg, traveler's diarrhea, Chapter 6) or pathogens (eg, malaria, Chapter 10). Constantly updated, current information for travelers about prophylaxis and current worldwide infection risks can be found on the Centers for Disease Control and Prevention Web site at www.cdc.gov/travel (accessed September 1, 2015).

## NOTE

- **Abbreviations:** AHA, American Heart Association; ALT, alanine aminotransferase; amox/clav, amoxicillin/clavulanate; ARF, acute rheumatic fever; bid, twice daily; CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; div, divided; DOT, directly observed therapy; GI, gastrointestinal; HSV, herpes simplex virus; IGRA, interferon-gamma release assay; IM, intramuscular; INH, isoniazid; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus;* N/A, not applicable; PCR, polymerase chain reaction; PO, orally; PPD, purified protein derivative; qd, once daily; qid, 4 times daily; spp, species; TB, tuberculosis; tid, 3 times daily; TIG, tetanus immune globulin; TMP/SMX, trimethoprim/sulfamethoxazole; UTI, urinary tract infection.

## A. POSTEXPOSURE SHORT-TERM ANTIMICROBIAL PROPHYLAXIS

| Prophylaxis Category | Therapy (evidence grade) | Comments |
|---|---|---|
| **Bacterial** | | |
| **Bites, animal and human**[1–4] (*Pasteurella multocida* [animal], *Eikenella corrodens* [human], *Staphylococcus* spp, and *Streptococcus* spp) | Amox/clav 45 mg/kg/day PO div tid (amox/clav 7:1; see Chapter 1 for amox/clav description) for 3–5 days (AII) OR ampicillin and clindamycin (BII). For penicillin allergy, consider ciprofloxacin (for *Pasteurella*) plus clindamycin (BIII). | Recommended for children who are (1) immunocompromised; (2) asplenic; (3) have moderate to severe injuries, especially to the hand or face; or (4) have injuries that may have penetrated the periosteum or joint capsule (AII).[3]<br>Consider rabies prophylaxis for animal bites (AI)[5]; consider tetanus prophylaxis.[6]<br>Human bites have a very high rate of infection (do not close open wounds routinely).<br>Cat bites have a higher rate of infection than dog bites.<br>*Staphylococcus aureus* coverage is only fair with amox/clav and provides no coverage for MRSA. |
| **Endocarditis Prophylaxis**[7]**:** Given that (1) endocarditis is rarely caused by dental/GI procedures and (2) prophylaxis for procedures prevents an exceedingly small number of cases, the risks of antibiotics most often outweigh benefits. However, some "highest risk" conditions are currently recommended for prophylaxis: (1) prosthetic heart valve (or prosthetic material used to repair a valve); (2) previous endocarditis; (3) cyanotic congenital heart disease that is unrepaired (or palliatively repaired with shunts and conduits); (4) congenital heart disease that is repaired but with defects at the site of repair adjacent to prosthetic material; (5) completely repaired congenital heart disease using prosthetic material, for the first 6 months after repair; or (6) cardiac transplant patients with valvulopathy. Routine prophylaxis no longer is required for children with native valve abnormalities. Follow-up data suggest that following these new guidelines, no increase in endocarditis has been detected.[8] | | |
| – In highest-risk patients: dental procedures that involve manipulation of the gingival or periodontal region of teeth | Amoxicillin 50 mg/kg PO 1 h before procedure OR ampicillin or ceftriaxone or cefazolin, all at 50 mg/kg IM/IV 30–60 min before procedure | If penicillin allergy: clindamycin 20 mg/kg PO (60 min before) or IV (30 min before) OR azithromycin 15 mg/kg or clarithromycin 15 mg/kg (1 h before) |
| – Genitourinary and gastrointestinal procedures | None | No longer recommended |

## A. POSTEXPOSURE SHORT-TERM ANTIMICROBIAL PROPHYLAXIS (continued)

| Prophylaxis Category | Therapy (evidence grade) | Comments |
|---|---|---|
| **Bacterial** (continued) | | |
| **Meningococcus** (*Neisseria meningitidis*)[9] | For prophylaxis of close contacts, including household members, child care center contacts, and anyone directly exposed to the patient's oral secretions (eg, through kissing, mouth-to-mouth resuscitation, endotracheal intubation, endotracheal tube management) in the 7 days before symptom onset<br>Rifampin<br>Children <1 mo: 5 mg/kg PO q12h for 4 doses<br>Children >1 mo: 10 mg/kg PO q12h for 4 doses (max 600 mg/dose) OR<br>Ceftriaxone<br>Children <15 y: 125 mg IM once<br>Children ≥16 y: 250 mg IM once OR<br>Ciprofloxacin 500 mg PO once (adolescents and adults) | A single dose of ciprofloxacin should not present a significant risk of cartilage damage, but no prospective data exist in children for prophylaxis of meningococcal disease. For a child, an equivalent exposure for ciprofloxacin to that in adults would be 15–20 mg/kg as a single dose (max 500 mg).<br>A few ciprofloxacin-resistant strains have now been reported.<br>Insufficient data to recommend azithromycin at this time. |
| **Pertussis**[10,11] | Same regimen as for treatment: Azithromycin 10 mg/kg/day qd for 5 days OR clarithromycin (for infants >1 mo) 15 mg/kg/day div bid for 7 days OR erythromycin (estolate preferable) 40 mg/kg/day PO div qid for 14 days (AII)<br>Alternative: TMP/SMX 8 mg/kg/day div bid for 14 days (BIII) | Prophylaxis to family members; contacts defined by CDC: persons within 21 days of exposure to an infectious pertussis case, who are at high risk of severe illness or who will have close contact with a person at high risk of severe illness (including infants, pregnant women in their third trimester, immunocompromised persons, contacts who have close contact with infants <12 mo). Close contact can be considered as face-to-face exposure within 3 feet of a symptomatic person; direct contact with respiratory, nasal, or oral secretions; or sharing the same confined space in close proximity to an infected person for ≥1 h. |

Community-wide prophylaxis is not currently recommended.

Azithromycin and clarithromycin are better tolerated than erythromycin (see Chapter 5); azithromycin is preferred in exposed young infants to reduce pyloric stenosis risk.

**Tetanus**
(*Clostridium tetani*)[12,13]

**NEED FOR TETANUS VACCINE OR TIG[a]**

| | Clean Wound | | Contaminated Wound | |
|---|---|---|---|---|
| Number of past tetanus vaccine doses | Need for tetanus vaccine | Need for TIG 250 U IM[a] | Need for tetanus vaccine | Need for TIG 250 U IM[a] |
| <3 doses | Yes | No | Yes | Yes |
| ≥3 doses | No (if <10 y[b])<br>Yes (if ≥10 y[b]) | No | No (if <5 y[b])<br>Yes (if ≥5 y[b]) | No |

[a] Intravenous immune globulin should be used when TIG is not available.
[b] Years since last tetanus-containing vaccine dose.

For deep, contaminated wounds, wound debridement is essential. For wounds that cannot be fully debrided, consider metronidazole 30 mg/kg/day PO div q8h until wound healing is underway and anaerobic conditions no longer exist, as short as 3–5 days (BIII).

## A. POSTEXPOSURE SHORT-TERM ANTIMICROBIAL PROPHYLAXIS (continued)

| Prophylaxis Category | Therapy (evidence grade) | Comments |
|---|---|---|
| **Bacterial** (continued) | | |
| **Tuberculosis** (*Mycobacterium tuberculosis*) Exposed children <4 y, or immunocompromised patient (high risk of dissemination)[14,15] For treatment of latent TB infection, see Table 14C. | Scenario 1: Previously uninfected child becomes exposed to a person with active disease. Exposed children <4 y, or immunocompromised patient (high risk of dissemination): INH 10–15 mg/kg PO daily for 2–3 mo after last exposure AND with repeat skin test or IGRA test negative (AIII). For older children, may also begin prophylaxis postexposure, but if exposure is questionable, can wait 2–3 mo after exposure; if repeat PPD/IGRA at 2–3 mo is positive at that time, start INH for 9-12 mo. | If PPD or IGRA remains negative at 2–3 mo and child remains well, consider stopping empiric therapy. However, tests at 2–3 mo may not be reliable in immunocompromised patients. This regimen is to prevent infection in a compromised host after exposure, rather than to treat latent asymptomatic infection. |
| | Scenario 2: Asymptomatic child is found to have a positive skin test/IGRA test for TB, documenting latent TB infection. INH 10–15 mg/kg PO daily for 9 mo (≥12 mo for an immunocompromised child) OR INH 20–30 mg/kg PO directly observed therapy twice weekly for 9 mo. | Other options For INH intolerance or INH resistance if a direct contact can be tested: rifampin 10 mg/kg PO daily for 4 mo For children ≥12 y, can use once weekly DOT with INH AND rifapentine for 12 wk; much less data for children 2–12 y[16] |
| **Viral** | | |
| **Herpes Simplex Virus** | | |
| During pregnancy | For women with recurrent genital herpes: acyclovir 400 mg PO bid; valacyclovir 500 mg PO qd OR 1 g PO qd from 36 wk gestation until delivery (CII)[17] | Development of neonatal HSV disease after maternal suppression has been documented. |

| | | |
|---|---|---|
| Neonatal: Primary or nonprimary maternal infection, infant exposed at delivery[18] | Asymptomatic, exposed infant: at 24 h of life, culture mucosal sites (see Comments), obtain CSF and whole-blood PCR for HSV DNA, obtain ALT, and start preemptive acyclovir IV (60 mg/kg/day div q8h) for 10 days (AII).<br>Some experts would evaluate at birth and start preemptive therapy. | Reference 18 provides a management algorithm that determines the type of maternal infection and, thus, the appropriate evaluation and preemptive therapy of the neonate.<br>Mucosal sites for culture: conjunctivae, mouth, nasopharynx, rectum.<br>Any symptomatic baby, at any time, requires a full evaluation for invasive infection and IV acyclovir therapy for 14–21 days. |
| Neonatal: Recurrent maternal infection, infant exposed at delivery[18] | Asymptomatic, exposed infant: at 24 h of life, culture mucosal sites, obtain whole-blood PCR for HSV DNA. Hold on therapy unless cultures or PCR are positive, at which time the diagnostic evaluation should be completed (CSF PCR for HSV DNA, serum ALT) and preemptive IV acyclovir (60 mg/kg/day div q8h) should be administered for 10 days (AIII). | Reference 18 provides a management algorithm that determines the type of maternal infection and, thus, the appropriate evaluation and preemptive therapy of the neonate.<br>Any symptomatic baby, at any time, requires a full evaluation for invasive infection and IV acyclovir therapy. Risk of neonatal HSV infection following inoculation (even if not documented by newborn evaluation) lasts 6–8 wk. |
| Neonatal: Following symptomatic disease, to prevent recurrence during first year of life[18] | 300 mg/m$^2$/dose PO tid for 6 mo following cessation of IV acyclovir treatment of acute disease (AI) | Follow absolute neutrophil counts at 2 and 4 wk, then monthly during prophylactic/suppressive therapy. |
| Keratitis (ocular) in otherwise healthy children | Suppressive therapy for frequent recurrence (no pediatric data): 20 mg/kg/dose bid (up to 400 mg) for 6–12 mo, then reevaluate need (AIII). | Based on data from adults. Anecdotally, some children may require tid dosing to prevent recurrences.<br>Check for acyclovir resistance for those who relapse while on appropriate therapy.<br>Watch for severe recurrence at conclusion of suppression. |

## A. POSTEXPOSURE SHORT-TERM ANTIMICROBIAL PROPHYLAXIS (continued)

| Prophylaxis Category | Therapy (evidence grade) | Comments |
|---|---|---|
| **Viral** (continued) | | |
| **Influenza virus (A or B)**[19] | Oseltamivir prophylaxis (AI)<br>3–≤8 mo: 3.0 mg/kg/dose qd for 10 days<br>9–11 mo: 3.5 mg/kg/dose PO bid qd for 10 days[20]<br>Based on body weight for children ≥12 mo<br>≤15 kg: 30 mg qd for 10 days<br>>15–23 kg: 45 mg qd for 10 days<br>>23–40 kg: 60 mg qd for 10 days<br>>40 kg: 75 mg qd for 10 days | Amantadine and rimantadine are not recommended for prophylaxis.<br>Not recommended for infants 0 to ≤3 mo unless situation judged critical because of limited data on use in this age group. |
| | Zanamivir prophylaxis (AI)<br>Children ≥5 y: 10 mg (two 5-mg inhalations) qd for as long as 28 days (community outbreaks) or 10 days (household settings) | |
| **Rabies virus**[21] | Rabies immune globulin, 20 IU/kg, infiltrate around wound, with remaining volume injected IM (AII).<br>Rabies immunization should be provided postexposure (AII). | For dog, cat, or ferret bite from symptomatic animal, immediate rabies immune globulin and immunization; otherwise, can wait 10 days for observation of animal, if possible, prior to rabies immune globulin or vaccine.<br>Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice and other rodents, rabbits, hares, and pikas almost never require antirabies prophylaxis.<br>For bites of bats, skunks, raccoons, foxes, most other carnivores, and woodchucks, immediate rabies immune globulin and immunization (regard as rabid unless geographic area is known to be free of rabies or until animal proven negative by laboratory tests). |

| Fungal | | |
|---|---|---|
| *Pneumocystis jiroveci* (previously *Pneumocystis carinii*)[22,23] | TMP/SMX as 5 mg TMP/kg/day PO, div 2 doses, q12h, either daily or 3 times/wk on consecutive days (AI); OR TMP/SMX 5 mg TMP/kg/day PO as a *single dose,* qd, given 3 times/wk on consecutive days (AI) (once-weekly regimens have also been successful); OR dapsone 2 mg/kg (max 100 mg) PO qd, or 4 mg/kg (max 200 mg) once weekly; OR atovaquone: 30 mg/kg/day for infants 1–3 mo; 45 mg/kg/day for infants 4–24 mo; and 30 mg/kg/day for infants >24 mo until no longer immunocompromised, based on oncology or transplant treatment regimen | Prophylaxis in specific populations based on degree of immunosuppression |

## B. LONG-TERM ANTIMICROBIAL PROPHYLAXIS TO PREVENT SYMPTOMATIC DISEASE

| Prophylaxis Category | Therapy (evidence grade) | Comments |
|---|---|---|
| **Bacterial otitis media**[24,25] | Amoxicillin or other antibiotics can be used in half the therapeutic dose qd or bid to prevent infections if the benefits outweigh the risks of (1) development of resistant organisms for that child and (2) the risk of antibiotic side effects. | To prevent recurrent infections, also consider the risks and benefits of placing tympanostomy tubes to improve middle ear ventilation.<br>Studies have demonstrated that amoxicillin, sulfisoxazole, and TMP/SMX are effective. However, antimicrobial prophylaxis may alter the nasopharyngeal flora and foster colonization with resistant organisms, compromising long-term efficacy of the prophylactic drug. Continuous PO-administered antimicrobial prophylaxis should be reserved for control of recurrent acute otitis media, only when defined as ≥3 distinct and well-documented episodes during a period of 6 mo or ≥4 episodes during a period of 12 mo. Although prophylactic administration of an antimicrobial agent limited to a period when a person is at high risk of otitis media has been suggested (eg, during acute viral respiratory tract infection), this method has not been evaluated critically. |
| **Acute rheumatic fever** | For >27.3 kg (>60 lb): 1.2 million U penicillin G benzathine, q4wk (q3wk for high-risk children)<br>For <27.3 kg: 600,000 U penicillin G benzathine, q4wk (q3wk for high-risk children)<br>OR<br>Penicillin V (phenoxymethyl) oral, 250 mg PO bid | AHA policy statement at http://circ.ahajournals.org/content/119/11/1541.full.pdf (accessed September 1, 2015).<br>Doses studied many years ago, with no new data; ARF an uncommon disease currently in the US. Alternatives to penicillin include sulfisoxazole or macrolides, including erythromycin, azithromycin, and clarithromycin. |
| **Urinary tract infection, recurrent**[26–29] | TMP/SMX 3 mg/kg/dose TMP PO qd OR nitrofurantoin 1–2 mg/kg PO qd at bedtime; more rapid resistance may develop using beta-lactams (BII). | Only for those with grade III–V reflux or with recurrent febrile UTI: prophylaxis no longer recommended for patients with grade I–II (some also exclude grade III) reflux and no evidence of renal damage. Prophylaxis prevents infection but may not prevent scarring. Early treatment of new infections is recommended for these children.<br>Resistance eventually develops to every antibiotic; follow resistance patterns for each patient. |

## C. PREEMPTIVE TREATMENT/LATENT INFECTION TREATMENT ("PROPHYLAXIS OF SYMPTOMATIC DISEASE IN CHILDREN WHO HAVE ASYMPTOMATIC INFECTION")

| | | |
|---|---|---|
| **Tuberculosis**[14,15]<br>(latent TB infection [asymptomatic infection], defined by a positive skin test or IGRA, with no clinical or x-ray evidence of active disease) | INH 10–15 mg/kg/day (max 300 mg) PO daily for 9 mo (12 mo for immunocompromised patients) (AII); treatment with INH at 20–30 mg twice weekly for 9 mo is also effective (AIII). | Single drug therapy if no clinical or radiographic evidence of active disease.<br>For exposure to known INH-resistant but rifampin-susceptible strains, use rifampin 10 mg/kg PO daily for 6 mo (AIII).<br>For children ≥12 y, can use once weekly DOT with INH AND rifapentine for 12 wk; much less data for children 2–12 y.[16]<br>For exposure to multidrug-resistant strains, consult with TB specialist. |

## D. SURGICAL/PROCEDURE PROPHYLAXIS[30–37]

The CDC and National Healthcare Safety Network use a classification of surgical procedure-related wound infections based on an estimation of the load of bacterial contamination: Class I, clean; Class II, clean-contaminated; Class III, contaminated; and Class IV, dirty/infected.[31,33] Other major factors creating risk for postoperative surgical site infection include the duration of surgery (a longer-duration operation, defined as one that exceeded the 75th percentile for a given procedure) and the medical comorbidities of the patient, as determined by an American Society of Anesthesiologists score of III, IV, or V (presence of severe systemic disease that results in functional limitations, is life-threatening, or is expected to preclude survival from the operation). The virulence/pathogenicity of bacteria inoculated and the presence of foreign debris/devitalized tissue/surgical material in the wound are also considered risk factors for infection.

For all categories of surgical prophylaxis, dosing recommendations are derived from (1) choosing agents based on the organisms likely to be responsible for inoculation of the surgical site; (2) giving the agents shortly before starting the operation to achieve appropriate serum and tissue exposures at the time of incision through the end of the procedure; (3) providing additional doses during the procedure at times based on the standard dosing guideline for that agent; and (4) stopping the agents at the end of the procedure but no longer than 24 to 48 h after the procedure.[32–34,36,37]

## D. SURGICAL/PROCEDURE PROPHYLAXIS[30–37] (continued)

| Procedure/Operation | Recommended Agents | Preoperative Dose | Re-dosing Interval (h) for Prolonged Surgery |
|---|---|---|---|
| **Cardiovascular** | | | |
| **Cardiothoracic**<br>*Staphylococcus epidermidis, Staphylococcus aureus, Corynebacterium* spp | Cefazolin, OR | 30 mg/kg | 4 |
| | Vancomycin, if MRSA likely[34] | 15 mg/kg | 8 |
| **Vascular**<br>*S epidermidis, S aureus, Corynebacterium* spp, gram-negative enteric bacilli, particularly for procedures in the groin | Cefazolin, OR | 30 mg/kg | 4 |
| | Vancomycin, if MRSA likely[34] | 15 mg/kg | 8 |
| **Gastrointestinal** | | | |
| **Gastroduodenal**<br>Enteric gram-negative bacilli, respiratory tract gram-positive cocci | Cefazolin | 30 mg/kg | 4 |
| **Biliary Procedure, Open**<br>Enteric gram-negative bacilli, enterococci, *Clostridia* | Cefazolin, OR | 30 mg/kg | 4 |
| | Cefoxitin | 40 mg/kg | 2 |
| **Appendectomy, non-perforated** | Cefoxitin, OR | 40 mg/kg | 2 |
| | Cefazolin and metronidazole | 30 mg/kg cefazolin and 10 mg/kg metronidazole | 4 for cefazolin<br>8 for metronidazole |
| **Complicated appendicitis or other ruptured viscus**<br>Enteric gram-negative bacilli, enterococci, anaerobes. May require additional therapy for treatment of infection. | Cefoxitin, OR | 40 mg/kg | 2 |
| | Cefazolin and metronidazole, OR | 30 mg/kg cefazolin and 10 mg/kg metronidazole | 4 for cefazolin<br>8 for metronidazole |
| | Meropenem, OR | 20 mg/kg | 4 |

| | | | |
|---|---|---|---|
| | Imipenem, OR | 20 mg/kg | 4 |
| | Ertapenem | 30 mg/kg | 8 |
| **Genitourinary** | | | |
| **Cystoscopy**<br>(only requires prophylaxis for children with suspected active UTI or those having foreign material placed)<br>Enteric gram-negative bacilli, enterococci | Cefazolin, OR | 30 mg/kg | 4 |
| | TMP/SMX (if low local resistance), OR<br>Select a 3rd-generation cephalosporin (cefotaxime) or fluoroquinolone (ciprofloxacin) if the child is colonized with cefazolin-resistant, TMP/SMX-resistant strains. | 4–5 mg/kg | N/A |
| **Open or laparoscopic surgery**<br>Enteric gram-negative bacilli, enterococci | Cefazolin | 30 mg/kg | 4 |
| **Head and Neck Surgery** | | | |
| Assuming incision through respiratory tract mucosa<br>Anaerobes, enteric gram-negative bacilli, *S aureus* | Clindamycin, OR | 10 mg/kg | 6 |
| | Cefazolin and metronidazole | 30 mg/kg cefazolin and 10 mg/kg metronidazole | 4 for cefazolin<br>8 for metronidazole |
| **Neurosurgery** | | | |
| Craniotomy, ventricular shunt placement<br>*S epidermidis, S aureus* | Cefazolin, OR | 30 mg/kg | 4 |
| | Vancomycin, if MRSA likely | 15 mg/kg | 8 |
| **Orthopedic** | | | |
| Internal fixation of fractures, spinal rod placement,[35] prosthetic joints<br>*S epidermidis, S aureus* | Cefazolin, OR | 30 mg/kg | 4 |
| | Vancomycin, if MRSA likely[34] | 15 mg/kg | 8 |

## D. SURGICAL/PROCEDURE PROPHYLAXIS[30–37] (continued)

| Procedure/Operation | Recommended Agents | Preoperative Dose | Re-dosing Interval (h) for Prolonged Surgery |
|---|---|---|---|
| **Trauma** | | | |
| Exceptionally varied; agents should focus on skin flora (*S epidermidis, S aureus*) as well as the flora inoculated into the wound, based on the trauma exposure, that may include enteric gram-negative bacilli, anaerobes (including *Clostridia* spp), and fungi. Cultures at time of wound exploration are critical to focus therapy. | Cefazolin (for skin), OR | 30 mg/kg | 4 |
| | Vancomycin (for skin), if MRSA likely, OR | 15 mg/kg | 8 |
| | Meropenem OR imipenem (for anaerobes, including *Clostridia* spp, and non-fermenting gram-negative bacilli), OR | 20 mg/kg for either | 4 |
| | Gentamicin and metronidazole (for anaerobes, including *Clostridia* spp, and non-fermenting gram-negative bacilli), OR | 2.5 mg/kg gentamicin and 10 mg/kg metronidazole | 6 for gentamicin<br>8 for metronidazole |
| | Piperacillin/tazobactam | 100 mg/kg piperacillin component | 2 |

## 15. Adverse Reactions to Antimicrobial Agents

A good rule of clinical practice is to be suspicious of an adverse drug reaction when a patient's clinical course deviates from the expected. This section focuses on reactions that may require close observation or laboratory monitoring because of their frequency or severity. For more detailed listings of reactions, review the US Food and Drug Administration (FDA)-approved package labels available at the National Library of Medicine (NLM) (http://dailymed.nlm.nih.gov, accessed September 1, 2015), with more recently approved agents actually having adverse events listed for the new agent and the comparator agent from the phase 3 prospective clinical trials. This allows one to assign drug-attributable side effects for specific drugs such as oseltamivir, used for influenza, when influenza and the antiviral may cause nausea. The NLM also provides an online drug information service for patients (MedlinePlus) at www.nlm.nih.gov/medlineplus/druginformation.html.

### Antibacterial Drugs

**Aminoglycosides.** Any of the aminoglycosides can cause serious nephrotoxicity and ototoxicity. Monitor all patients receiving aminoglycoside therapy for more than a few days for renal function with periodic determinations of blood urea nitrogen and creatinine to assess potential problems of drug accumulation with deteriorating renal function. Common practice has been to measure the peak serum concentration 0.5 to 1 hour after a dose to make sure one is in a safe and therapeutic range and to measure a trough serum concentration immediately preceding a dose to assess for drug accumulation and pending toxicity. Monitoring is especially important in patients with any degree of renal insufficiency. Elevated trough concentrations (>2 mg/mL for gentamicin and tobramycin; >10 mg/mL for amikacin) suggest drug accumulation and should be a warning to decrease the dose, even if the peak is not yet elevated. Renal toxicity may be related to the total exposure of the kidney to the aminoglycoside over time. With once-daily administration regimens, peak values are 2 to 3 times greater, and trough values are usually very low. Nephrotoxicity seems to be less common in adults with once-daily (as opposed to 3 times daily) dosing regimens, but data are generally lacking in children.[1] In patients with cystic fibrosis with pulmonary exacerbations, once-daily aminoglycosides appear less toxic and equally effective.[2]

The "loop" diuretics (furosemide and bumetanide) and other nephrotoxic drugs may potentiate the ototoxicity of the aminoglycosides. Aminoglycosides potentiate botulinum toxin neuromuscular junction dysfunction and are to be avoided in young infants with infant botulism.

Minor side effects, such as allergies, rashes, and drug fever, are rare.

**Beta-lactam Antibiotics.** The most feared reaction to penicillins, anaphylactic shock, is extremely rare, and no absolutely reliable means of predicting its occurrence exists. For most infections, alternative therapy to penicillin or beta-lactams exists. However, in certain situations, the benefits of penicillin or a beta-lactam may outweigh the

risk of anaphylaxis, requiring that skin testing and desensitization be performed in a medically supervised environment. The commercially available skin testing material, benzylpenicilloyl polylysine (Pre-Pen, AllerQuest), contains the major determinants thought to be primarily responsible for urticarial reactions but does not contain the minor determinants that are more often associated with anaphylaxis. No commercially available minor determinant mixture is available. For adults, the Centers for Disease Control and Prevention (CDC) suggests using a dilute solution of freshly prepared benzyl penicillin G as the skin test material in place of a standardized mixture of minor determinants (www.cdc.gov/std/treatment/2010/penicillin-allergy.htm, accessed September 1, 2015). Testing should be performed on children with a credible history of a possible reaction to a penicillin before these drugs are used in oral or parenteral formulations. Anaphylaxis has been reported in adults receiving penicillin skin testing. Recent reviews provide more in-depth discussion,[3,4] with additional information on desensitization available at the CDC Web site noted above. Cross-reactions between classes of beta-lactam antibiotics (penicillins, cephalosporins, carbapenems, and monobactams) occur at a rate of less than 5% to 20%, with the rate of reaction to cephalosporins in patients with a *history* of penicillin allergy of about 0.1%.[5] No commercially available skin-testing reagent has been developed for beta-lactam antibiotics other than penicillin.

Amoxicillin and other aminopenicillins are associated with minor adverse effects. Diarrhea, oral or diaper-area candidiasis, morbilliform, and blotchy rashes are not uncommon. The kinds of non-urticarial rashes that may occur while a child is receiving amoxicillin are not known to predispose to anaphylaxis and may not actually be caused by amoxicillin itself; they do not represent a routine contraindication to subsequent use of amoxicillin or any other penicillins. Rarely, beta-lactams cause serious, life-threatening pseudomembranous enterocolitis due to suppression of normal bowel flora and overgrowth of toxin-producing strains of *Clostridium difficile*. Drug-related fever may occur; serum sickness is uncommon. Reversible neutropenia and thrombocytopenia may occur with any of the beta-lactams and seem to be related to dose and duration of therapy but do not appear to carry the same risk of bacterial superinfection that is present with neutropenia in oncology patients.



The cephalosporins have been a remarkably safe series of antibiotics. Third-generation cephalosporins cause profound alteration of normal flora on mucosal surfaces, and all have caused pseudomembranous colitis on occasion. Ceftriaxone commonly causes loose stools, but it is rarely severe enough to require stopping therapy. Ceftriaxone in high dosages may cause fine "sand" (a calcium complex of ceftriaxone) to develop in the gallbladder. In adults, and rarely in children, these deposits may cause biliary tract symptoms; these are not gallstones, and the deposits are reversible after stopping the drug. In neonates receiving calcium-containing hyperalimentation concurrent with intravenous (IV) ceftriaxone, precipitation of ceftriaxone-calcium in the bloodstream resulting in death has been reported,[6] leading to an FDA warning against the concurrent use of ceftriaxone and parenteral calcium in neonates younger than 28 days. As ceftriaxone may also displace bilirubin from albumin-binding sites and increase free bilirubin in serum,

the antibiotic is not routinely used in neonatal infections until the normal physiologic jaundice is resolving after the first few weeks of life. Cefotaxime is the preferred IV third-generation cephalosporin for neonates.

Imipenem/cilastatin, meropenem, and ertapenem have rates of adverse effects on hematopoietic, hepatic, and renal systems that are similar to other beta-lactams. However, children treated with imipenem for bacterial meningitis were noted to have an increase in probable drug-related seizures not seen with meropenem therapy in controlled studies.[7] For children requiring carbapenem therapy, meropenem is preferred for those with any underlying central nervous system inflammatory condition.

**Fluoroquinolones (FQs).** All quinolone antibiotics (nalidixic acid, ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin) cause cartilage damage to weight-bearing joints in toxicity studies in various immature animals; however, no conclusive data indicate similar toxicity in young children. Studies to evaluate cartilage toxicity and failure to achieve predicted growth have not consistently found statistically significant differences between those children treated with FQs and controls, although in an FDA-requested, blinded, prospective study of complicated urinary tract infections, the number of muscular/joint/tendon events was greater in the ciprofloxacin-treated group than in the comparator (www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM162536.pdf, accessed September 1, 2015). This continues to be an area of active investigation by the pediatric infectious disease community as well as the FDA. Fluoroquinolone toxicities in adults, which vary in incidence considerably between individual agents, include cardiac dysrhythmias, hepatotoxicity, and photodermatitis; other reported side effects include gastrointestinal symptoms, dizziness, headaches, tremors, confusion, seizures, and alterations of glucose metabolism producing hyperglycemia and hypoglycemia. The American Academy of Pediatrics published a clinical report on the use of fluoroquinolones and, based on the best available evidence, concluded that IV fluoroquinolones should be used when safer IV antibiotic alternatives were not available and that oral fluoroquinolones should be used if no other safe and effective oral therapy existed, even if effective alternative IV therapy existed.[8]

**Lincosamides.** Clindamycin can cause nausea, vomiting, and diarrhea. Pseudomembranous colitis due to suppression of normal flora and overgrowth of *C difficile* is uncommon, especially in children, but potentially serious. Urticaria, glossitis, pruritus, and skin rashes occur occasionally. Serum sickness, anaphylaxis, and photosensitivity are rare, as are hematologic and hepatic abnormalities. Extensive use of clindamycin since 2000 for treatment of community-associated methicillin-resistant *Staphylococcus aureus* infections has not been accompanied by reports of significantly increasing rates of *C difficile*–mediated colitis in children.

**Macrolides.** Erythromycin is one of the safest antimicrobial agents but has largely been replaced by azithromycin because of substantially decreased epigastric distress and nausea. Alteration of normal flora is generally not a problem, but oral or perianal candidiasis occasionally develops. Intravenous erythromycin lactobionate causes phlebitis

and should be administered slowly (1–2 hours); the gastrointestinal side effects seen with oral administration also accompany IV use. However, IV azithromycin is better tolerated than IV erythromycin and has been evaluated for pharmacokinetics in limited numbers of children.[9]

Erythromycin therapy has been associated with pyloric stenosis in newborns and young infants; due to this toxicity and with limited data on safety of azithromycin in the first months of life, azithromycin is now the preferred macrolide for treatment of pertussis in neonates and young infants.[10]

**Oxazolidinones.** Linezolid represents the first oxazolidinone antibiotic approved for all children, including neonates, by the FDA. Toxicity is primarily hematologic, with thrombocytopenia and neutropenia that is dependent on dosage and duration of therapy, occurring most often with treatment courses of 2 weeks or longer. Routine monitoring for bone marrow toxicity every 1 to 2 weeks is recommended for children on long-term therapy. Peripheral neuropathy and optic neuritis may also occur with long-term therapy.[11]

**Sulfonamides and Trimethoprim.** The most common adverse reaction to sulfonamides is a hypersensitivity rash. Stevens-Johnson syndrome, a life-threatening systemic reaction characterized by immune-mediated injury to the skin and mucous membranes, occurs in approximately 3 of 100,000 exposed people. Neutropenia, anemia, and thrombocytopenia occur occasionally. Sulfa drugs can precipitate hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency. Drug fever and serum sickness are infrequent hypersensitivity reactions. Hepatitis with focal or diffuse necrosis is rare. A rare idiosyncratic reaction to sulfa drugs is acute aseptic meningitis.

**Tetracyclines.** Tetracyclines are used infrequently in pediatric patients because the major indications are uncommon diseases (rickettsial infections, brucellosis, Lyme disease), with the exception of acne. Tetracyclines are deposited in growing bones and teeth, with depression of linear bone growth, dental staining, and defects in enamel formation in deciduous and permanent teeth. This effect is dose related, and the risk extends up to 8 years of age. A single treatment course of tetracyclines has not been found to cause dental staining, leading to the recommendation for tetracyclines as the drugs of choice in children for a number of uncommon pathogens. Doxycycline is likely to produce less dental staining than tetracycline. A parenteral tetracycline approved for adults in 2005, tigecycline, produces the same "staining" of bones in experimental animals as seen with other tetracyclines.

Side effects include minor gastrointestinal disturbances, photosensitization, angioedema, glossitis, pruritus ani, and exfoliative dermatitis. Potential adverse drug reactions from tetracyclines involve virtually every organ system. Hepatic and pancreatic injuries have occurred with accidental overdosage and in patients with renal failure. (Pregnant women are particularly at risk for hepatic injury.)

**Vancomycin.** Vancomycin can cause phlebitis if the drug is injected rapidly or in concentrated form. Vancomycin has the potential for ototoxicity and nephrotoxicity, and serum concentrations should be monitored for children on more than a few days of therapy. Hepatic toxicity is rare. Neutropenia has been reported. If the drug is infused too rapidly, a transient rash of the upper body with itching may occur from histamine release (red man syndrome). It is not a contraindication to continued use and the rash is less likely to occur if the infusion rate is increased to 60 to 120 minutes and the children are pretreated with oral or IV antihistamines.

**Daptomycin.** This antibiotic is still undergoing investigation in children; therefore, the full adverse event profile is not yet available, but data presented at national/international meetings do not indicate adverse events that occur in children that have not been reported in adults. Specifically, no drug-attributable muscle toxicity or elevated creatine kinase concentrations have been reported. Of concern, prior to clinical studies in infants younger than 1 year, neonatal puppy studies indicated the possibility of the development of neurotoxicity in the first days of life; therefore, studies in infants younger than 1 year are not being performed. These concerns are presented in the current FDA-approved package label.

### Antituberculous Drugs

Isoniazid (INH) is generally well tolerated and hypersensitivity reactions are rare. Peripheral neuritis (preventable or reversed by pyridoxine administration) and mental aberrations from euphoria to psychosis occur more often in adults than in children. Mild elevations of alanine transaminase in the first weeks of therapy, which disappear or remain stable with continued administration, are common. Rarely, hepatitis develops but is reversible if INH is stopped; if INH is not stopped, liver failure may develop in these children. Monitoring of liver functions is not routinely required in children receiving INH single drug therapy for latent tuberculosis as long as the children can be followed closely and liver functions can be drawn if the children develop symptoms of hepatitis.

Rifampin can also cause hepatitis; it is more common in patients with preexisting liver disease or in those taking large dosages. The risk of hepatic damage increases when rifampin and INH are taken together in dosages of more than 15 mg/kg/day of each. Gastrointestinal, hematologic, and neurologic side effects of various types have been observed on occasion. Hypersensitivity reactions are rare.

Pyrazinamide also can cause hepatic damage, which again seems to be dosage related. Ethambutol has the potential for optic neuritis, but this toxicity seems to be rare in children at currently prescribed dosages. Young children who cannot comment to examiners about color blindness or other signs of optic neuritis should have an ophthalmologic examination every few months on therapy. Optic neuritis is usually reversible.

## Antifungal Drugs

Amphotericin B (deoxycholate) causes chills, fever, flushing, and headaches, the most common of the many adverse reactions. Some degree of decreased renal function occurs in virtually all patients given amphotericin B. Anemia is common and, rarely, hepatic toxicity and neutropenia occur. Patients should be monitored for hyponatremia, hypomagnesemia, and hypokalemia. However, much better tolerated (but more costly) lipid formulations of amphotericin B are now commonly used (see Chapter 2). For reasons of safety and tolerability, the lipid formulations should be used whenever possible.

Fluconazole is usually very well tolerated from clinical and laboratory standpoints. Gastrointestinal symptoms, rash, and headache occur occasionally. Transient, asymptomatic elevations of hepatic enzymes have been reported but are rare.

Voriconazole may interfere with metabolism of other drugs the child may be receiving due to hepatic P450 metabolism. However, a poorly understood visual field abnormality has been described, usually at the beginning of a course of therapy and uniformly self-resolving, in which objects appear to glow. There is no pain and no known anatomic or biochemical correlate of this side effect; no lasting effects on vision have yet been reported. Hepatic toxicity has also been reported but is not so common as to preclude the use of voriconazole for serious fungal infections. Phototoxic skin reaction with chronic use that has been reported to develop into carcinoma is another common reason for discontinuation.[12,13]

Caspofungin, micafungin, and anidulafungin (echinocandins) are very well tolerated as a class. Fever, rash, headache, and phlebitis at the site of infection have been reported in adults. Uncommon hepatic side effects have also been reported.

Flucytosine (5-FC) is seldom used due to the availability of safer, equally effective therapy. The major toxicity is bone marrow depression, which is dosage related, especially in patients treated concomitantly with amphotericin B. Renal function should be monitored.

## Antiviral Drugs

After extensive clinical use, acyclovir has proved to be an extremely safe drug with only rare serious adverse effects. Renal dysfunction with IV acyclovir has occurred mainly with too rapid infusion of the drug. Neutropenia has been associated with administration of parenteral and oral acyclovir but is responsive to granulocyte colony-stimulating factor use and resolves spontaneously following temporary halting of the drug. At very high doses, parenteral acyclovir can cause neurologic irritation, including seizures. Rash, headache, and gastrointestinal side effects are uncommon. There has been little controlled experience in children with famciclovir and valacyclovir.

Ganciclovir causes hematologic toxicity that is dependent on the dosage and duration of therapy. Gastrointestinal disturbances and neurologic damage are rarely encountered. Oral valganciclovir can have these same toxicities as parenteral ganciclovir, but neutropenia is seen much less frequently following oral valganciclovir compared with IV ganciclovir.

Oseltamivir is well tolerated except for nausea with or without vomiting, which may be more likely to occur with the first few doses but usually resolves within a few days while still on therapy. Neuropsychiatric events have been reported, primarily from Japan, in patients with influenza treated with oseltamivir (a rate of approximately 1:50,000) but also are seen in patients on all of the other influenza antivirals and in patients with influenza receiving no antiviral therapy. It seems that these spontaneously reported side effects may be a function of influenza itself, oseltamivir itself, possibly a genetic predisposition to this clinical event, or a combination of all 3 factors.

Foscarnet can cause renal dysfunction, anemia, and cardiac rhythm disturbances. Alterations in plasma minerals and electrolytes occur, and any clinically significant metabolic changes should be corrected. Patients who experience mild (eg, perioral numbness or paresthesia) or severe (eg, seizures) symptoms of electrolyte abnormalities should have serum electrolyte and mineral levels assessed as close in time to the event as possible.

## 16. Drug Interactions

### NOTES

- Antimicrobial drug-drug interactions that are known to be clinically significant and likely to be encountered in children are listed in this chapter. Interactions involving probenecid, synergy-antagonism, and in vitro physical incompatibilities are not listed. Interactions involving antiretrovirals can be found at www.aidsinfo.nih.gov. Interactions involving QT interval prolongation can be found at www.crediblemeds.org. Common antimicrobials with an increased risk of QT interval prolongation include azole antifungals, macrolides, fluoroquinolones, and trimethoprim/sulfamethoxazole. Cited references at the end of this section provide more extensive details of all reported and theoretical interactions, including antimicrobial drug-disease interactions.
- Erythromycin, clarithromycin, and the azole antifungals inhibit cytochrome P450 (CYP) enzyme activity and interact with numerous drugs. Cytochrome P450 inhibition can increase the concentration of the interacting drug and cause toxicity. Fluconazole and posaconazole are relatively weak CYP inhibitors, but even they have many significant interactions. Drug transporter protein inhibition is another source of some azole interactions. Conversely, enzyme-inducing antiepileptic drugs and rifamycins are inducers of CYP activity and can reduce an interacting drug's concentration and efficacy.
- **Abbreviations:** ACE, angiotensin-converting enzyme; conc, concentration; CYP, cytochrome P450; decr, decreased; EIAED, enzyme-inducing antiepileptic drug; incr, increased; INR, international normalized ratio; IV, intravenous; MAO, monoamine oxidase; NSAID, nonsteroidal anti-inflammatory drug; PGP, p-glycoprotein; PO, orally; PPI, proton pump inhibitor; TMP/SMX, trimethoprim/sulfamethoxazole.

| Anti-infective Agent | Interacting Drug(s) | Adverse Effect |
|---|---|---|
| Acyclovir/valacyclovir | Nephrotoxins,[a] ceftriaxone | Additive nephrotoxicity |
| Amantadine | Anticholinergics,[b] trimethoprim | Neurotoxicity |
| Aminoglycosides[c] (parenteral) | Nephrotoxins[a] | Additive nephrotoxicity |
| | Neuromuscular blocking agents | Incr neuromuscular blockade |
| | Indomethacin, ibuprofen | Incr aminoglycoside conc |
| | Carboplatin/cisplatin | Additive ototoxicity |
| Amphotericin B | Nephrotoxins[a] | Additive nephrotoxicity |
| | Cisplatin, corticosteroids, diuretics | Additive hypokalemia |
| Atovaquone | Metoclopramide, rifamycins, tetracycline | Decr atovaquone conc |
| Carbapenems | Valproic acid | Decr valproic acid conc |
| Caspofungin | Cyclosporine | Incr caspofungin conc, hepatotoxicity |
| | Tacrolimus, sirolimus | Decr conc of interacting drug |
| | Rifampin, EIAEDs[d] | Decr caspofungin conc |
| Cefdinir | Iron, antacids | Decr cefdinir oral absorption |
| Cefpodoxime, cefuroxime PO | Antacids, $H_2$ antagonists, PPI | Decr anti-infective oral absorption |
| Ceftriaxone, IV | Calcium, IV | Precipitation, cardiopulmonary embolism |
| | Acyclovir, nephrotoxins[a] | Additive nephrotoxicity |
| Ciprofloxacin | Caffeine, theophylline, sildenafil, warfarin | Incr conc of interacting drug |
| | Phenytoin | Decr conc of phenytoin |
| | Antacids, bismuth, calcium, iron, sucralfate, zinc | Decr ciprofloxacin oral absorption[e] |
| Clindamycin | Neuromuscular blocking agents | Incr neuromuscular blockade |
| Doxycycline | Antacids, bismuth, calcium, iron, sucralfate, zinc | Decr doxycycline oral absorption[e] |
| | EIAEDs,[d] rifamycins | Decr doxycycline conc |

| Anti-infective Agent | Interacting Drug(s) | Adverse Effect |
|---|---|---|
| Erythromycin, clarithromycin[f] | CYP 3A4 substrates[g] | Incr conc of interacting drug |
| | Rifamycins | Decr anti-infective conc |
| Fluconazole[h] | Cyclosporine, cyclophosphamide, fentanyl, alfentanil, methadone, midazolam, NSAIDs, omeprazole, phenytoin, sirolimus, tacrolimus, warfarin | Incr conc of interacting drug |
| | EIAEDs,[d] rifampin | Decr fluconazole conc |
| Griseofulvin | EIAEDs[d] | Decr griseofulvin conc |
| Isavuconazole[f] | CYP 3A4 substrates[g] | Incr conc of interacting drug |
| Isoniazid | Acetaminophen, carbamazepine | Hepatotoxicity |
| | Antacids | Decr isoniazid conc |
| | Carbamazepine, phenytoin, valproic acid, warfarin | Incr conc of interacting drug |
| | Antidepressants, linezolid, sympathomimetics | MAO inhibition toxicity, hypertensive reaction |
| Itraconazole, ketoconazole[f,i] | CYP 3A4 substrates[g] | Incr conc of interacting drug |
| | Antacids, $H_2$ antagonists, PPI | Decr azole absorption, itraconazole oral solution less affected, voriconazole not affected |
| | EIAEDs,[d] rifamycins | Decr azole conc |
| | Digoxin (with itraconazole) | Incr digoxin conc (inhibition of PGP transport) |
| Linezolid | Antidepressants, isoniazid, sympathomimetics | MAO inhibition toxicity, hypertensive reaction |
| Metronidazole | Busulfan, 5-fluorouacil, phenytoin, warfarin | Incr conc of interacting drug |
| | EIAEDs[d] | Decr metronidazole conc |
| Nafcillin | Warfarin | Decr warfarin effect, decr INR |
| Oritavancin | Heparin | Unreliable coagulation markers |
| Penicillins | Methotrexate | Incr methotrexate conc |

| Anti-infective Agent | Interacting Drug(s) | Adverse Effect |
|---|---|---|
| Posaconazole | Antacids, $H_2$ antagonists, PPI | Decr absorption of oral posaconazole |
| | Midazolam, sirolimus, tacrolimus, vincristine | Incr conc of interacting drug |
| | EIAEDs[d] | Decr posaconazole conc |
| Rifampin, rifabutin | Numerous CYP and transporter substrates | Decr conc of interacting drug |
| Terbinafine | Antidepressants, β-blockers | Incr conc of interacting drug |
| Tetracycline | Isotretinoin | Intracranial hypertension |
| TMP/SMX | Amantadine, methotrexate, phenytoin, warfarin | Incr conc of interacting drug |
| | ACE inhibitors, spironolactone | Additive hyperkalemia |
| Vancomycin | Indomethacin, ibuprofen | Incr vancomycin conc |
| Voriconazole[f] | CYP 3A4 substrates[g] | Incr conc of interacting drug |
| | EIAEDs,[d] rifamycins | Decr voriconazole conc |
| | See also fluconazole.[j] | |

[a] Examples of nephrotoxic drugs: ACE inhibitors, acyclovir, aminoglycosides, cidofovir, contrast agents, cyclosporine, diuretics, foscarnet, NSAIDs, pentamidine, polymyxins, tacrolimus, vancomycin.

[b] Examples of anticholinergics: atropine, belladonna, dicyclomine, diphenhydramine, glycopyrrolate, hyoscyamine, promethazine, scopolamine.

[c] Gentamicin, tobramycin, amikacin, streptomycin.

[d] EIAEDs: carbamazepine, phenobarbital, phenytoin, and primidone.

[e] Class-wide effect; interaction will also occur with other fluoroquinolones (levofloxacin, moxifloxacin) and tetracyclines (minocycline).

[f] CYP 3A4 inhibitor; may inhibit CYP 3A4 substrates (see footnote g).

[g] CYP 3A4 substrates: alfentanil, antineoplastics (known interactions with busulfan, cyclophosphamide, docetaxel, irinotecan and vinca alkaloids, many others possible; see Ruggiero et al), benzodiazepines (CYP 3A4 oxidized benzodiazepines: alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, midazolam, and triazolam), bosentan, carbamazepine, cyclosporine, dexamethasone, erythromycin/clarithromycin, fentanyl, loratadine, methadone, methylprednisolone, sildenafil, sirolimus, tacrolimus, tiagabine.

[h] Fluconazole interactions mediated mainly by CYP 2C9, 2C19, and some 3A4 inhibition.

[i] Ketoconazole is also known to have or may potentially have the same interactions as fluconazole due to similar inhibition of CYP 2C9 and CYP 2C19 drug metabolism.

[j] Interaction profile is similar to fluconazole due to similar CYP inhibition.

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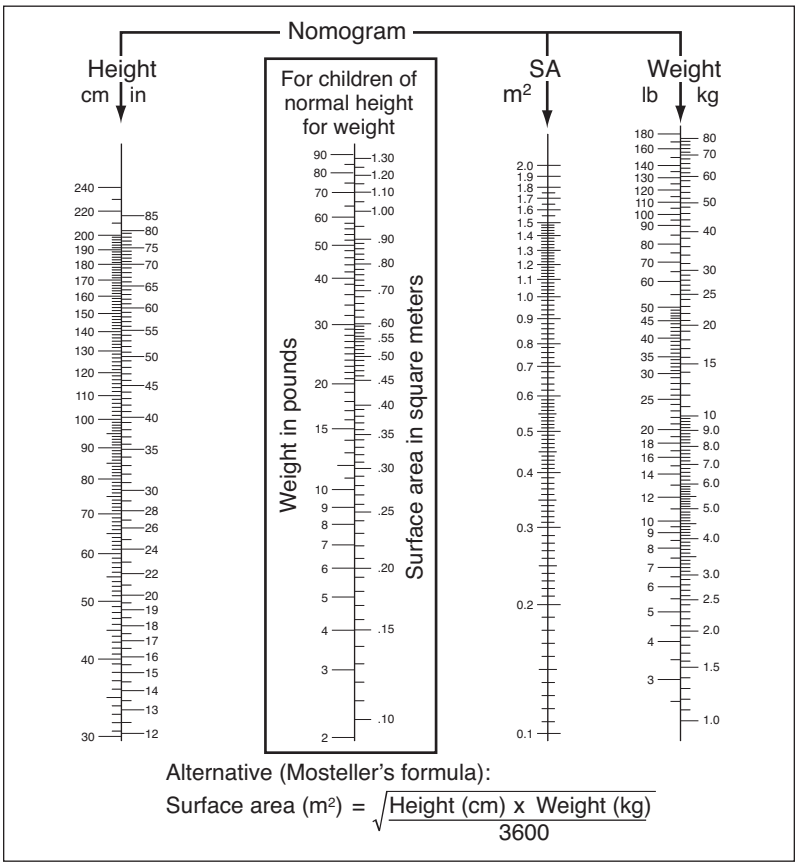
# Appendix

## Nomogram for Determining Body Surface Area

Based on the nomogram shown below, a straight line joining the patient's height and weight will intersect the center column at the calculated body surface area (BSA). For children of normal height and weight, the child's weight in pounds is used, and then the examiner reads across to the corresponding BSA in meters. Alternatively, Mosteller's formula can be used.




Nomogram and equation to determine body surface area. (From Engorn B, Flerlage J, eds. *The Harriet Lane Handbook.* 20th ed. Philadelphia, PA: Elsevier Mosby; 2015. Reprinted with permission from Elsevier.)

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